The FDA's Draft Process Validation Guidance – A Perspective from Industry

by Nuala Calnan, Alice Redmond, and Stan O'Neill

This article provides an overview of the draft guidance, the key changes in relation to the 1987 guidance, and reviews its potential impact on the current industry approaches to science- and risk-based design and qualification activities which support the process validation program.

Abstract

The long anticipated draft of the FDA's *Guidance for Industry* on Process Validation should be welcomed for the clarity of its integrated three stage lifecycle process, its emphasis on the need for effective scientific knowledge led programs, and the elimination of the "Three Golden Batches" concept.

Introduction

In November 2008, the FDA published the long anticipated draft of its *Guidance for Industry* on "Process Validation: General Principles and Practices." This draft, which has just completed its public comment period, will replace the FDA's 1987 "Guideline on General Principles of Process Validation" when finalized and represents the FDA's current thinking in regard to process validation. It sets out the approaches that the FDA consider to be appropriate elements of process validation for the manufacture of human and veterinary drugs, including biologicals and APIs. No specific mention is made within the scope to investigational medicinal products or medical devices, for which CDRH has published its own guidance through the Global Harmonization Task Force.

This article provides an overview of the draft guidance, the key changes in relation to the 1987 guidance, and reviews its potential impact on the current industry approaches to science- and risk-based design and qualification activities which support the process validation program.

Basic Principles of Quality Assurance

Effective **Process Validation** contributes significantly to assuring drug quality.

The basic principle of **Quality Assurance** is that a drug should be produced that **is fit for its intended use**; this principle incorporates the understanding that the following conditions exist:

- Quality, safety, and efficacy are designed or *built* into the product.
- Quality *cannot be adequately assured* merely by in-process and finished-product inspection or testing.
- Each step of a manufacturing process is controlled to assure that the finished product meets all design characteristics and quality attributes including specifications.

Ref: Guidance for Industry Process Validation: General Principles and Practices (Nov 2008).

The Lifecycle Approach

The guidance states at the outset that it has been written to promote "*modern manufacturing principles, process improvement, innovation, and sound science*" and is significantly aligned with the ***Product Lifecycle Approach*** described in the ICH Guidance Q8 (R1), Q9, and Q10[1] and the Quality by Design (QbD) initiative. This lifecycle approach emphasizes the importance of the links between the following:

1. product and process design and development
2. qualification of the commercial manufacturing equipment and process
3. maintenance of the process in a state of control during routine commercial production

Continued on page 10.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2009,
Vol. 29 No. 3

DeltaV Batch.

The perfect cup. Every time.

Easy.

Emerson understands your need to quickly respond to varying customer requirements. That's why we designed DeltaV Batch to give you the robust, repeatable performance that lets you assure your customers of a perfect, on-spec batch. First time. Every time. Easy.

From seamless integration with your enterprise planning and manufacturing execution systems to modular, class-based configuration and integrated change management, DeltaV Batch simplifies your batch operations.

Enabling agile manufacturing has never been easier. So, grab yourself a fresh cup and visit: **EasyDeltaV.com/Batch**

DeltaV™

EMERSON.™
Process Management

EMERSON. CONSIDER IT SOLVED.™

Three Stages of Process Validation

Process validation involves a series of activities taking place over the lifecycle of the product and process.

Stage 1 – Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
Stage 2 – Process Qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.
Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

Ref: Guidance for Industry Process Validation: General Principles and Practices (Nov 2008).

One of the key messages from this draft is that validation of the process is not a "one off" event, but represents an ongoing continuum of scientific knowledge development and ongoing assurance. There is a real emphasis throughout the draft on the importance of acquiring this knowledge about the process from the early process design stage right throughout commercial manufacture, which is a significant departure from the convention of (essentially) testing the process outputs. Success relies on the establishment of a comprehensive science-based process design, which focuses on understanding the sources of variability in achieving process understanding and recognizes that more knowledge will be gained during product commercialization. The draft emphasizes that the key to this success will lie in an organizations proficiency "in the collection and evaluation of information and data about the performance of the process," and outlines specific guidance relating to the use of quantitative statistical methods to enhance understanding of process performance.

From this, the guidance defines Process Validation activities in three stages identified in Figure 1.

Key tenets of the lifecycle approach outlined are:

- A manufacturer should have gained a high degree of assurance in the performance of the manufacturing process before any batch from the process is commercially distributed for use by consumers.
- This assurance should be obtained from objective information and data from laboratory, pilot, and/or commercial scale studies – this implies a need for greater scrutiny of process performance during the early stages of commercial manufacture.
- A successful validation program depends upon the skilled interpretation of the information and knowledge gained from product and process development regarding sources of variation, its impacts, and the associated risks.
- This knowledge and understanding is cited as the basis for establishing the appropriate control strategy for the manufacturing process.
- The product and process design and development information is then used to develop the approach to process validation, and the scientific knowledge is verified by testing (in-process, release, characterization) of each significant step of the commercial manufacture process.
- The significant emphasis in the lifecycle is on maintaining the process in a state of control over the life of the process, which will require ongoing data analysis of both intra-batch and inter-batch variability, and appropriate provisions to address deviations and nonconforming data.
- It emphasizes the importance of both QA professionals and line operators in providing feedback for continued process verification.
- Not surprisingly, the guidance focuses on the importance of demonstrating, documenting, and utilizing process understanding in designing effective validation programs. It provides a strong lead in acknowledging that qualification programs devoid of process understanding will not guarantee the assurance of quality required.

Significant Recommendations

The main body of the guidance is provided under section IV *Recommendations,* where very useful general considerations on the three stages of process validation and their associated activities are outlined.

This is where we see the most significant alignment with current industry thinking for implementation of science- and risk-based lifecycle approaches and where the most significant departures from the prescriptive approaches of the 1987 guidance are noted.

Under **"General Considerations for Process Validation,"** it emphasizes the importance of making the entire process validation program more effective and efficient through the following:

- good project management
- robust scientific knowledge collection, management, and archiving
- uniform collection and assessment of information methods
- reducing the burden of redundant information gathering
- use of an integrated team approach

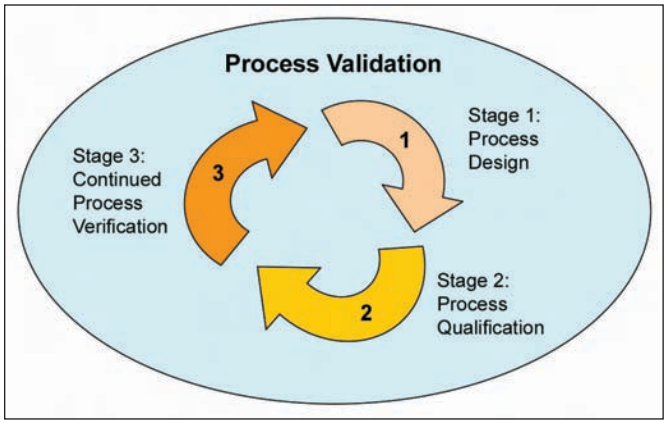
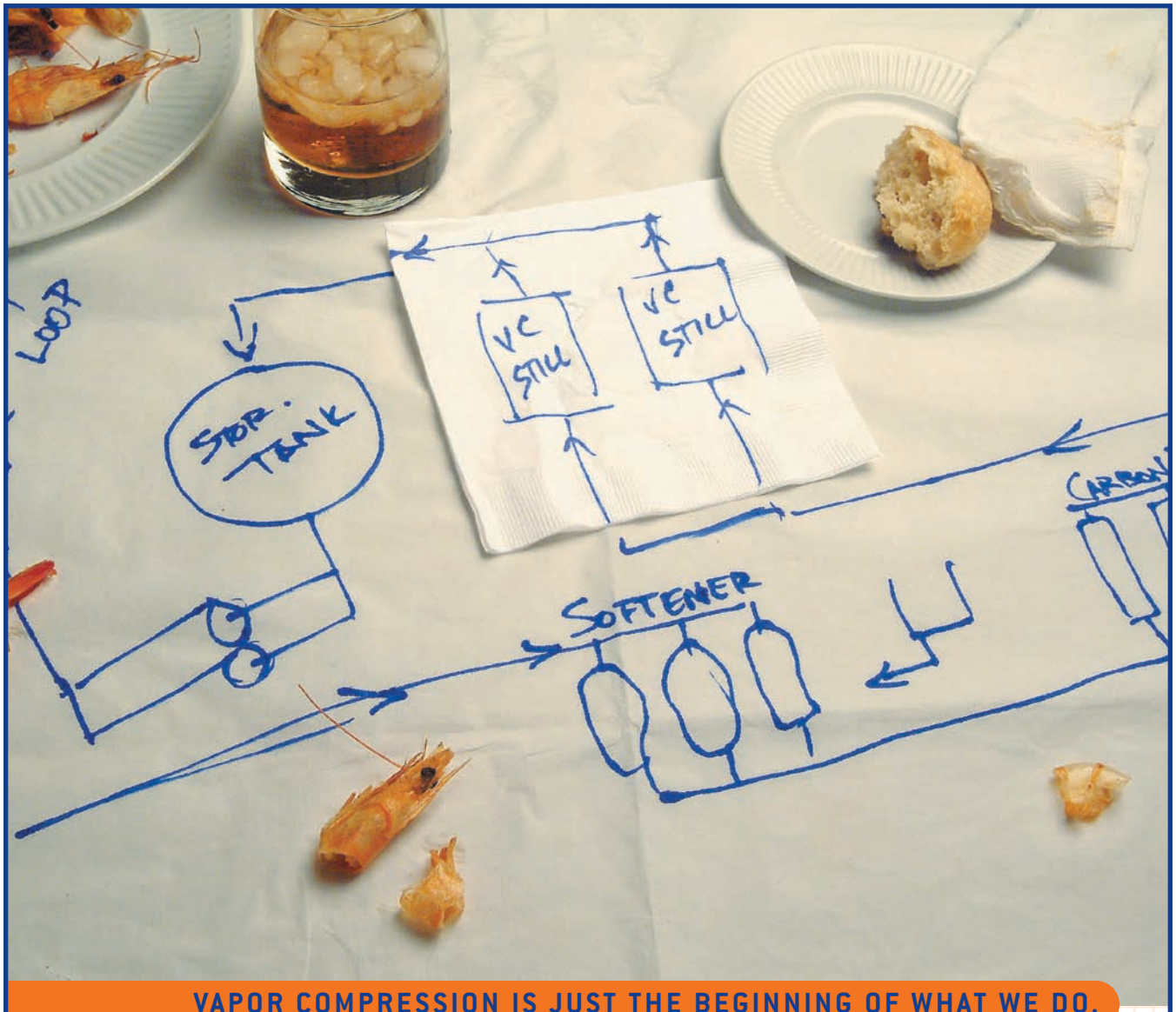


Figure 1. Process validation lifecycle activities shown in three stages.

Continued on page 12.



VAPOR COMPRESSION IS JUST THE BEGINNING OF WHAT WE DO.

Innovative Solutions For Purified And WFI-Grade Water And Pure Steam.

It was a big idea that simply got bigger. Today, MECO has grown to provide expert guidance and customized solutions for every phase of water and Pure Steam generation. Whether you need a particular product, a specialized service or an entire water plant designed and built from scratch, MECO delivers. To see for yourself, visit mecobiopharm.com or call 1-800-421-1798.

MECO

MECO NO BOUNDARIES PROMISE

PEOPLE | PRODUCTS | SERVICE

US _ UK _ Singapore _ UAE _ 800-421-1798 _ mecobiopharm.com

12505 Reed Road, Suite 100, Sugar Land, TX 77478

Key Definition: Process Validation (PV)

*"The collection and evaluation of data, from the process design stage throughout production, which establishes **scientific evidence** that a process is capable of consistently delivering quality products"*

Ref: Guidance for Industry Process Validation: General Principles and Practices (Nov 2008).

- appropriately documented Project Plans
- the support of senior management
- statistical assessment of data

The draft recommends the "integrated team approach" as presented in the FDA's 2006 guidance entitled, "Quality Systems Approach to Pharmaceutical Current Manufacturing Principles," involving expertise from a variety of disciplines, including process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance. Furthermore, both here and throughout the document, it emphasizes the need for effective and efficient programs and supports the move away from overly bureaucratic traditional qualification practices and in doing so provides good alignment with the key principles of the recent ASTM standard E2500-07.[2]

In "Specific Stages and Activities of Process Validation in the Product Lifecycle," the guidance gives specific direction on each of the three stages of process validation.

Stage 1: Process Design

The stated goal of this stage is to *"design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its Critical Quality Attributes (CQAs)."* The guidance again makes reference to ICH Q10, Pharmaceutical Quality Systems, and draws some distinctions around the varying levels of controls required related to the product development lifecycle activities.

The focus of this stage is on developing methods and competencies for building and capturing process knowledge and understanding and in using this scientific knowledge as the basis for establishing an approach to effective process control. It states that the *"Design of Experiment (DOE) studies can help develop process knowledge by revealing relationships, including multi-factorial interactions, between the variable inputs (e.g., component characteristics or processing parameters) and the resulting outputs (e.g., in-process material, intermediates, or the final product)."* Risk analysis tools can be used to minimize the total number of experiments conducted while maximizing knowledge gained. The results of the DOE studies should be used to establish ranges of incoming component quality, equipment parameters, and in process material quality attributes.

The draft draws attention to the recent advances with Process Analytical Technology (PAT), which may be used for real time analysis, facilitating control loops to adjust the processing conditions so that the process output remains constant and reproducible. However, it does indicate that in the case of PAT, the approach to process qualification will be different from that for other process designs by focusing on the qualification of the measurement system and control loop.

Significantly, by grouping the recommendations for product and process design together in this stage, it further endorses an integrated approach. Within this integrated approach, while it acknowledges that the full spectrum of input variability typical of the commercial production is not generally known at this stage, it directly recommends that the team responsible for process design take early consideration of the functionality and limitations of commercial manufacturing equipment by utilizing their knowledge about measurement systems in a production setting, contributions to process variability from different raw materials or component lots, production operators or environmental conditions. This ethos will no doubt be welcomed by many involved in the start up of regulated commercial manufacturing facilities who have dealt with the challenges posed when this early integration of commercial production and process design has not been successful.

Stage 2: Process Qualification

This stage of the process validation lifecycle is undoubtedly going to generate the most comment and perhaps lead to some initial confusion, due to its use and definition of terminology relating to *Process* and *Performance* qualification.

The stated goal of this key stage is that *"the process design is confirmed as being capable of reproducible commercial manufacture."* The guidance further divides this stage into the following two elements:

1. design of the facility and qualification of the equipment and utilities
2. Performance Qualification (PQ)

Stage 2-1: Design of the Facility and Qualification of Utilities and Equipment

This section of the guidance opens with a welcome reference to the essential role that proper facility design and commissioning play in the start-up of a facility and cites them as prerequisites to the commencement of PQ.

Most significantly, the guidance gives a key definition for qualification as shown below:

The draft guidance states that qualification of utilities and equipment generally includes the following activities:

Key Definition: Qualification

"Activities undertaken to demonstrate that utilities and pieces of equipment are suitable for their intended use and perform properly is referred to in this guidance as qualification"

Ref: Guidance for Industry Process Validation: General Principles and Practices (Nov 2008).

Continued on page 14.

ELETTRACQUA

pure water technologies

SINCE 1966

PHARMACEUTICAL WATER SYSTEMS

DOUBLE PASS REVERSE OSMOSIS HIGH TEMPERATURE SANITIZATION

DESIGN AND CONSTRUCTION OF PURIFIED WATER PACKAGES ♦ DOUBLE PASS REVERSE OSMOSIS ♦ R.O. + ELECTRODEIONIZATION HOT WATER SANITIZABLE ♦ ULTRAFILTRATION ♦ MULTIPLE - EFFECT DISTILLATION UNITS ♦ PURE STEAM GENERATORS ♦ STORAGE AND DISTRIBUTION LOOP ♦ COMPLETE TURN KEY PROJECTS ♦ VALIDATIONS IQ, OQ

www.elettracqua.com

visit us at
ACHEMA 2009
Frankfurt am Main/Germany
11.–15. 5. 2009
hall 4.1 - stand L20/L22

- selecting utilities and equipment based on whether they are appropriate for their specific use
- verifying that the utility system and equipment are built/installed in compliance with the design specifications and operate in accordance with the process requirements in all anticipated operating ranges for routine production
- challenging the equipment or system functions while under loads comparable to that expected during routine production
- performance of interventions, stoppage, and start-up as is expected during routine production

The guidance requires that these *qualification* activities are covered either under an individual plan or as part of an overall project plan. In line with the ICH Q9, Quality Risk Management guidance, the plan should consider the use of risk management to prioritize certain activities and to identify the appropriate level of effort for both the performance and the documentation of these qualification activities.

Finally, it confirms the requirement for the *qualification* activities to be documented in a report with conclusions that specifically address the criteria set out in the plan. It is important to note this draft's expectation that the quality control unit must review and approve both the qualification plan and the report. There is divergence here with the recently published ASTM E2500-07[2] standard, which seeks Quality Unit preapproval of the qualification acceptance criteria rather than the plan, but concurs on the Quality Unit post approval of the qualification report.

Stage 2-2: Performance Qualification (PQ)

Performance Qualification (PQ) is the phrase used to described the second element of the overall process qualification and combines the actual qualified facility, utilities, and commercial manufacturing process equipment with the trained personnel using cGMP compliant control procedures (SOPs), and all raw materials and components necessary to produce commercial batches.

The use of the phrase Performance Qualification (PQ) in the context of producing commercial batches may present divergence from what is widely understood to be within the scope of a "traditional" PQ, which currently focuses on equipment and process performance for clean utilities, cleaning, and sterilization processes. In the 1987 guide, this was described as *Process Performance Qualification* and was distinguished from that which was referred to as *Product Performance Qualification*. This draft combines the two efforts within this stage in order to achieve the stated goal of overall *Performance Qualification (PQ)* which is to *"confirm the process design and demonstrate that the commercial manufacturing process performs as expected."*

Success at this stage is cited as an important milestone in the product lifecycle and must be completed before a manufacturer commences commercial distribution of the drug product.

The draft requires that the design of the PQ study should ensure that:

- The manufacturing conditions set for the PQ are established based on the cumulative data from all relevant studies (e.g., designed experiments; laboratory, pilot, and commercial batches).
- Objective measures (e.g., statistical metrics) are used to evaluate the outputs and justify that adequate assurance has been achieved.
- Greater scrutiny of process performance is undertaken during PQ through the use of enhanced levels of sampling and testing. This enhanced level of monitoring and testing should be capable of confirming uniform product quality is achieved throughout the batch during processing.

It will be important to understand and assess the impact of these expectations relating to PQ early in the overall lifecycle as they may affect process development activities, system design, equipment selection, or team selection considerations and will certainly influence the development of methods and procedures.

In relation to the number of PQ batches required, to date product PQ was typically followed by the traditional "three PV batches." Now no fixed number of new PQ batches are prescribed and manufacturers must provide justification for any rationale used in asserting that assurance has been achieved. However, it is noted that the words "commercial batches" are used, which would suggest the use of more than one batch.

Furthermore, it is important to note the expectation that the greater scrutiny accompanied by the enhanced level of sampling undertaken during the PQ batches should continue initially into the continued process verification stage.

Of particular note in the document is the recommendation that the PQ lots should be manufactured under normal conditions. Thus, a matrix approach with extremes of operating conditions is not expected for this phase of validation.

The guidance provides specific recommendations on the format and content of the PQ protocol and the report including as follows:

- manufacturing conditions, such as operating parameters, process limits, and raw materials inputs are documented
- details of the data to be collected, including when and how it is evaluated
- details of the in-process, release, and characterization tests to be performed, as well as the acceptance criteria for each significant step
- the sampling plan, including sampling points, the number of samples, and the frequency of sampling for each unit operation, based on statistical confidence incorporating risk analysis
- criteria showing the processes consistently produce quality batches, including a description of the statistical methods used to define both intra-batch and inter-batch variability, and provisions to address deviations and nonconforming data
- design of facilities and qualification of utilities and equip-

1987 PV Guidance	2008 Draft
Defines validation as "establishing documented evidence"	Defines validation in terms of "establishing scientific evidence"
Principles of quality assurance wording revision from "cannot be inspected or tested into the finished product"	to "cannot be adequately assured merely by in-process and finished product inspection or testing"
Principles of quality assurance wording revision from "designed and built into the product"	to "is designed or built"
Wording revision from "maximize the probability that"	to "is controlled to assure"
	Introduction of "integrated team approach"
	Introduction of "product lifecycle" concept
	exclusion of "revalidation" and "retrospective process validation"
	Introduction of Process Analytical Technology (PAT) concepts for PV
	Introduction of "root cause" (e.g., review of customer complaints and impact on process)
	Removes validation information for medical devices
	Emphasizes Science Based Knowledge development
	Emphasizes the use of qualitative statistical methods to monitor, evaluate and justify assurance of process performance

Table A. Key changes between 1987 PV Guidance and 2008 Draft.

ment, training, and verification of source materials
- validation status of analytical methods used to measure the process, materials, and product
- review and approval by the appropriate department and the quality unit

Finally, the draft elaborates on the opportunities presented for manufacturers utilizing PAT systems to support activities undertaken in the next stage.

Stage 3: Continued Process Verification

The stated goal of the third process validation stage is to *"continually assure that the process remains in a state of control (the validated state) during commercial manufacture."* This will require robust systems for detecting unplanned departures (drift) from the designed process, and there is a strong emphasis on the use of statistically trended data, which is reviewed in a timely manner by trained personnel, such as statisticians or persons with adequate training in statistical process control techniques.

The development of a Data Collection Plan is recommend ensuring that the information collected can verify that the critical quality attributes are being controlled throughout the process.

This production data also should evaluate process stability and capability and the scrutiny should include both intra-batch as well as inter-batch variation. The quality unit should evaluate this data, discuss possible trends or drifts in the process, and coordinate any correction or follow-up actions with production personnel.

As referred to previously, the draft recommends that the enhanced monitoring and/or sampling initially established during the process qualification stage continue until sufficient data is available to generate significant variability estimates and justification, using statistical metrics, is available to support their relaxation.

It is noted that data gathered during this stage may identify ways to improve and/or optimize the process and appropriate procedures to control and manage these changes must be in

Concludes on page 16.

place. It highlights that maintenance of the facility, utilities, and equipment is another important aspect of ensuring that a process remains in control. While the document discusses the use of continued process verification to identify variability and improve the process, no mention is made to the possible implications on already commercialized batches.

Finally, it states a fundamental tenet that following the scientific based approach requires that information transparency and accessibility are essential so that organizational units responsible for the process can make informed, science-based decisions that ultimately support the ongoing commercial release of a product.

Conclusion

It is the opinion of the authors that this guide will be welcomed for many reasons, primarily for the clarity and simplicity of the integrated three stage lifecycle process, but also for the emphasis on the need for effective and efficient science-based programs, which seek to reduce unnecessary duplication in activities through the application of product and process knowledge throughout the lifecycle.

From a facility, utility, and equipment qualification perspective the welcomed avoidance of traditional, prescriptive terminology such as DQ, IQ, and OQ offer teams real opportunities to look behind the prepared templates and design and execute qualification and validation programs which are not only valid, but valuable to the ongoing operation and continuous improvement. There is only one minor exception to this relating to an external cross reference in the introduction to the very prescriptive validation approach for APIs found in the ICH Q7A guidance. This is likely to add confusion rather than clarity and which hopefully will be dealt with through the public comment phase.

Upon first review, this draft in itself does not appear to have any new implications for the preparation and submission of regulatory filings.

However, for many organizations, aligning this FDA process validation guidance with the current EMEA legislative requirements and recommendations for process validation would be very beneficial.[3]

Finally, from an ISPE Technical Documents perspective, due to the revised use of terminology and the welcome step back from prescriptive qualification practices, final publication of this guidance will provide an opportunity to review several current ISPE Guidance documents for alignment. This will impact both the Baseline® Pharmaceutical Engineering Guides series and Good Practices Guide series, many of which are already under revision for alignment with recent ICH guidance.

References

1. See the FDA/International Conference on Harmonisation (ICH) guidance for industry:
   a. Q8 Pharmaceutical Development
   b. Q9 Quality Risk Management
   c. Q10 Pharmaceutical Quality Systems
2. ASTM E2500-07: Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment, July 2007.
3. Notes for Guidance on Process Validation; CPMP/QWP/848/96, EMEA/CVMP/598/99 September 2001.

About the Authors

Nuala Calnan is a Principal Consultant with PM Group, Ireland and has more than 17 years of experience in the pharmaceutical industry. Currently, she is a member of the ISPE International Board of Directors and was a member of the Author Task Team which produced the recent ASTM E2500-07 International Standard. Calnan also is a member of the document development task team currently writing the *ISPE Baseline Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment*. She graduated in 1991 with a BSc in engineering (BSc Eng) and achieved her MBA in 2002. She is a regular contributor at ISPE conferences. She can be reached by telephone: 353-14040700 or by email: nuala.calnan@pmg.ie.

PM Group, Kilakee House, Belgard Square, Tallaght, Dublin 24, Ireland.

Alice Redmond is CQ Technical Director with PM Group, has more than 20 years of experience in the R&D, pharmaceutical (API, formulation fill, solid dosage), and biotechnology industry. She graduated with a BSc in biotechnology in 1987, a PhD in biotechnology in 1991 and a MBs in 2001. Current responsibilities include oversight of regulatory compliance, GEP, quality, commissioning, qualification and validation strategies on a corporate level for PM Group. Redmond is an active member of ISPE and PDA. She co-chaired and presented at the ISPE GEP ICQ Conference in Copenhagen in 2006, and the Singapore ISPE Conference in July 2008. She can be contacted by telephone: 353-214358922 or by email: alice.redmond@pmg.ie.

PM Limited, Loughmahon Technology Park, Blackrock, Cork, Ireland.

Stan O'Neill is the Managing Director of the Compliance Group. After qualifying as a pharmacist, he spent more than five years working in the pharmaceutical industry in Regulatory Affairs, marketing, and Quality Assurance (QP), and then joined the Irish Medicines Board (IMB) for a period of 10 years. In his capacity as a Senior Inspector, he performed GMP inspections throughout the world, represented Ireland at European level for the negotiation of standards of inspection for medicinal products, and trained Inspectors at Irish, European, and International levels. He can be contacted by telephone: 353-866032297 or by email: stanoneill@compliancegroup.eu

The Compliance Group, 22 Earlsfort Terrace, Dublin 2, Ireland.

Expertise right down the line

Glatt granulation line

Perfected manufacturing of high density granules in a single production system is one example of Glatt's core competence.

As always, state-of-the-art: Glatt's vertical granulator in combination with Glatt's efficient fluid-bed dryer is a proven technology for manufacturing high density wet granules. Modular configuration is available with the addition of wet and dry sieves. Granulation lines from Glatt incorporate 2-bar venting or are available with our unique closed 12-bar safety design. Glatt has the perfect solution for every application.

- Clear advantages due to the maximum safety design, optimum handling and minimum space requirements
- Horizontal or vertical product flow configurations available
- No intermediate explosion safety devices required for the entire granulation line thanks to the 12-bar safety system
- SC SuperClean®: fully automated, CIP cleaning system with validation
- Intelligent multipanel control design
- Optional through-the-wall design

Fluid Bed Systems

Vertical Granulators

Product Handling

Pan Coaters

Engineering

Services

Glatt Air Techniques Inc.
20 Spear Road
Ramsey, NJ 07446 / USA
Phone: +1 201 8 25 87 00
Fax: +1 201 8 25 03 89
eMail: info@glattair.com

Glatt GmbH Process Technology
Werner-Glatt-Straße 1
79589 Binzen / Germany
Phone: +49 7621 6 64 0
Fax: +49 7621 6 47 23
eMail: info@glatt.com

www.glatt.com

Glatt®

PE / 1SPE – MAY / JUNE 2009 – NEUBERGER.DESIGN

This article presents the questions and answers from a recent ISPE Webinar focused on the FDA's draft process validation guidance.

The Draft Process Validation Guidance – A Perspective from the FDA

Introduction

In January 2009 Grace McNally of the US FDA provided a first time public view and understanding on the new draft *Guidance for Industry – Process Validation* in a live ISPE Webinar. Paul D'Eramo, Executive Director, Johnson & Johnson, hosted a question and answer session which gave attendees the chance to submit their questions and have them directly answered by McNally. The following is a transcript of some of the highlights of that Q&A session:

Q Do we have any idea on when it might get finalized?

A Once we get the comments in we'll have to empanel a group of experts to evaluate them, make some decisions, write responses, and adopt suggestions if appropriate or not. I can't tell you exactly how long that process will take but it's certainly our intention to get that done and get a final published this year, 2009.

Q Did you discuss this draft with other regulatory bodies such as in Europe, to see what their reaction might be in regards to harmonizing some of their documents?

A No, this was an FDA effort only and it did not involve other regulatory agencies. Certainly, it's available to them. I've been to conferences where representatives from other regulatory bodies have asked about it, so they are aware that it was in draft. Of course, it's on the Web and it's available for everybody to take a look at and comment on.

Q It's clear in the document you've referenced Q8, Q9, and Q10. It's not as clear as how this relates to Q7, especially because there are sections in Q7 that discuss validation. So should we defer to that?

A Yes, Q7A has a very prescriptive specific section about validation. That is the standard for APIs. If there appears to be any conflict between that and this guidance, I would certainly ask that you submit those comments to us and we will consider them as we revise the guidance for final.

Q When you implement this, is there a plan for how you will be training the FDA investigators to make sure everybody's consistent?

A Yes, that's a very good question. We haven't done that in a formal comprehensive way. We have the basic drug school or courses geared toward our pharmaceutical inspectorate. Myself and others involved in this working group have given talks about this new guidance – it wasn't published because we weren't distributing it at that point – and the concepts in it, discussing the principles and how they should be thinking about process validation, which isn't terribly different than the thinking we had under the 1987 guidelines. A careful reading of the 1987 guidelines is very revealing. It is not fundamentally different in its basic principles.

But yes, the investigative staff will need to be trained and we will be developing a formal training program. Certainly this is just a draft and there may be revisions, so we are not prepared to do that quite yet until we have the final. As far as the implementation phase, it's important to remember that this is a guidance, it's not a regulation. These are recommendations. This is the current thinking about what we believe are useful practices for process validation in this day and time. So an implementation phase doesn't really apply to this guidance.

Q How does this guide relate to the aseptic processing guide? Does that processing guide take precedent for sterile products?

Continued on page 20.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2009,
Vol. 29 No. 3

In safe hands

Containment Solutions for the Pharmaceutical & Biotech Industries

- Barrier Isolation Systems
- Downflow Containment Booths
- High Containment Screens
- Pack Off and Process Equipment
- Kilo Labs & Glassware Enclosures



howorth
air technology

For further information please contact us on
North America 502 968 2065
Rest of the World +44 (0) 1204 571131
info@howorthgroup.com www.howorthgroup.com

A Yes, that's a good point. The aseptic processing guide is as direct and prescriptive for that activity and that manufacturing operation. So if there is a guidance out there that specifically addresses a type of manufacturing activity, that is what you want to look at. This guidance is not intended to conflict with the aseptic processing guide or any of the guidances out there. I know in the biological realm there are specific guidances for viral clearance or other technical manufacturing aspects and those should be your primary reference.

Q Can you explain the major differences between the old guide and the new as it relates to existing (or legacy) products? For example, if we have to revalidate an existing product, should I use the new guideline or the old principles?

A Process validation is a lifecycle and if you're in a position of revalidating, for whatever reason... I would direct your attention to Stage 3. If you have an existing product in process and you're revalidating it, I would assume there's been some trigger for that. It would make sense to me that the trigger for that is information you gathered during what we're calling Stage 3, commercialization activities that you do under 211.180 (e), part of your periodic evaluation. (That information) brought to your attention something that needs to be changed or checked. So it would make sense at that point to incorporate the principles in this new guidance. And remember they're not that different. If I was to go back, and I do have the old guideline here in front of me, it also calls for a maintenance of a state of control.

So I would say good companies concerned about quality are going to use revalidation for whatever the impetus was... to adopt a modern view. As a company you also want to be philosophically congruent. If companies are embracing an attitude of continuous improvement it seems to me that that would permeate their thinking for all their product lines. Now, having said that I'm not saying if you have an old process that is performing well, and there's no indication, there's no quality indicator data that suggests to you something is amiss, I'm not suggesting that you run out and begin R&D all over for each of these product and process lines.

It would make sense to me that as part of your overall quality system, and certainly as part of the periodic evaluation of all product lines, that whatever your procedures dictate that you consider each of these products and processes as part of your periodic evaluation procedures. You can certainly take for example, you may want to consider some sort of risk analysis of each of your product lines and processes and see what can and should be done to improve them if that appears necessary, based our your data and evaluation. There's no move afoot on our part to send investigative teams out to go through a company's product line, find the five year old process that seems to be doing quite well and start digging into R&D records … that's not the goal and it won't be part of any action on the field's part.

But I would say to you as the company to think about your processes and product lines. You do and are required and certainly want to have in place these periodic evaluation procedures. So when an older and existing process comes up, my question then to you, is do you think you should apply these new principles. And they're really not that new actually. I would recommend that everybody who is concerned about this new guidance being different than the old should sit down with the new one and the old one and carefully read them.

Q Someone made the comment, it seems our industry lags somewhat in process monitoring/statistical process control. It is now clear that this is an expectation. Another asks, can you use Six Sigma concepts to rationalize process validation being in a state of control. Can you elaborate on that Continued Verification, Stage 3, the monitoring part, and how you foresee that?

A While it's true that references to statistical criteria and procedures are prominently featured in this guidance, I will say that that's not new … It's a topic that we need to shine light on and put on the table. It is my belief that it has been somewhat ignored as of late. Certainly it has to be wrestled with. It raises a lot of questions about how to do this.

But I would say it really is not new. I'm looking at the old guidance, second to last section. It's talking about testing, test data, and ...process monitoring. It says, "specific results on the other hand can be statistically analyzed and a determination can be made of what variance and data can be accepted." So those ideas have been around for a long time. In Stage 3, you can use Six Sigma. We're not going to prescribe what statistical tools to use and really we're just looking for a scientific basis and objective measures, and statistics are one of them.

In this day and age, I understand from many people in industry that there are a lot of good software packages out there and they can be very valuable. And even in Stage 2, you have limited data at that point and so the power of those analyses may not be as great because you have much more accumulative data in Stage 3, once you're making a lot of commercial batches … but they would be very useful. We're not going to dictate which statistical tools to use, but you as a company should select what works for you and be able to defend why it's scientific and objective.

Q Was a there a reason why risk analysis was not discussed in the document?

A Yes, we made a deliberate effort to not explore topics that have already been thoroughly covered in other guidelines or guidances. Risk management is thoroughly discussed in ICH Q9 and we've referenced it. But to avoid retread on already established concepts – we mention it and there is an expectation that risk analysis will be used throughout the lifecycle and all of the stages – felt it was not necessary to go into detail. That is expected, and

use the guidances available on it.

Q Will a glossary be added? There are terms such as process verification and product performance. Criticality is not really defined anywhere. Do you think you'll go back and put some of those terms into a glossary?

A A few thoughts on criticality. We actually in our earlier versions used the word critical throughout the document. The definition of criticality has been greatly debated. We've seen many definitions, whether individual companies prefer a definition, whether a regulatory body has a certain slant on their definition. In the interest of getting this guidance done, we did not put a glossary in because so many of the terms are debatable in terms of what they mean. Criticality, we took out of there and went back to our source document which is the GMP and chose to use the word "significant." So you'll see in those places that term instead of criticality.

But the comment about the glossary in general, there isn't a glossary. But if the comments we get back strongly suggest that that is indispensible or absolutely necessary in order to prevent confusion or make this guidance meaningful and useful then we'll take that into consideration.

And I should just say as an aside, there's no magic to the terminology that we chose to use for this guidance: Stage 1, Stage 2, Stage 3. They're just terms we chose and then laid out what they meant. That's something each of your individual companies probably do as well. Certainly there's value in everybody using and having the same meaning but to expect that to happen, I wouldn't bet money on it. I think the key about terminology is, whenever you get involved in a discussion with somebody, whether it's in an audit, or your collaborating on something, as long as that group understands what is meant by certain terms, then you can make progress and have a successful meeting or inspection, or move forward. But the glossary issue, I would say we will look at that in terms of the comments that we get back from everybody.

Q Is there value in executing PQ at ranges versus a target or should this be carried out in the development phase?

A That's a great question and that really speaks to the old guideline. In the old guideline you certainly get the impression that the boundary conditions (worst case challenges, edge of the operating parameters that have been established, whatever you want to call it, edge of operating limits) in the old guidance to me and my reading of it is that that's something you're going to do as your making commercial batches, this performance qualification stage or what we would call it, Stage 2. It seems to me that while that knowledge should be pursued, it would make sense that that would be in the Stage 1 arena, or I should at least say, it's not something you want to do when you're ultimately confirming your process design and working with product you intend to sell. I would agree with the inquiry statement that before you ready what you think is commercial product you've probably already explored that and have some understanding of what those limits are and what their impact is on the product quality and process. I agree that you would want to explore that up front.

Q Please elaborate on the following – "to have sufficient understanding of the commercial process, the manufacturer will need to consider the effects of scale; however, it is not typically necessary to explore the entire operating range at commercial scale if assurance can be provided by other data." Can you clarify what is sufficient understanding and what is the agency's thinking there and the same for scale? Does this need to be done at full scale batches?

A ...as far as sufficient data, there are certain words that the Agency will use, such as "appropriate" or "sufficient." Because it's going to differ from company to company and product to product… it's a judgment call that the manufacturer must make and then be able to explain why they feel this is adequate from a science perspective...

Concludes on page 22.

the key there, is people will talk in terms of how many commercial size batches do I have to make. The more important question is, having made these batches, however many there are, what is it that you're looking (for). That's the criteria. That's what you want to specify in your protocol, your plan. The real question is, but what about them, what are you doing with them, what is the data you're looking at, what is the information? Is it during processing, are you looking at the controls and the process parameters, how tight they are or not. Are you looking at attributes of the in-process material in the final product and what about it, are you going to do some analysis of that data. It's not about the number of batches, it's what data are you gleaning and how are you handling that data and what are your expectations.

Q Does the Continued Process Verification Program for a given drug product require formal protocol, similar in fashion to Performance Qualification? Should this data be collected, analyzed, summarized (and approved) by the QA – Validation Department?

A That's a very good question. I am not saying it's required but it makes rational sense. If you have a new product or process for which you don't have a lot of history and you don't have a similar product or process from which you could leverage information; I think that's one of the holes in the way things are operated right now. You have the pre-approval and post-approval and it goes from getting approval and launch to automatically, oversight is at routine levels. Well the routine levels may not be appropriate immediately.

To answer this person's question, it's not required, but I think it's an excellent idea, sort of a transition; things aren't on and off, like flipping a light switch. And I suspect companies don't just say it's a new process, and so now once it's approved we'll just treat it like the one that's been running for three years seamlessly. I think there is more oversight and appropriately so.

So under Stage 3 I can envision and would certainly recommend that you would have formal protocols, or at least a procedure. I don't want to say protocol because I don't want to give people the idea that this is what you have to do. But doesn't it make sense, if you're going to assess performance over time, to establish some criteria and some sort of procedure and then execute it, gather that data and do those analyses. And put numbers, I mean that's mainly where we're coming from, the statistics that you see in this new guidance are "objective measures," I think it maybe only says it once in there. But if you're going to assert that you have confidence in this unit operation, this process overall, this particular attribute, can you put a number on it. I think more and more today you can if you use the right tools.

Confidence intervals, how sure am I about this data point or this statistical metric I just calculated. How confident am I. It's going to depend on sample size, it's going to depend on a lot of things. But you can put a label on how confident you are on some of your data … I think this inquirer's insight is a fine one and makes sense. Again, Stage 3, if you're trying to maintain things in a state of control you want to be able to measure what it's doing, what is that process doing over time. It's really the essence of that 211.180 (e), Periodic Evaluation, when you say you're doing a Periodic Evaluation, what tools are you employing to do that. So really what the inquirer is getting at is what tools do we want to devise to do our Periodic Evaluation. I think it's a great idea.

Q You purposely did not use the number three in batches in the document, but there are a few questions asking if it would be appropriate to mention a minimum number?

A Here's the key word you have to think about. You have to demonstrate reproducibility. As far as a minimum number, again it's not the number of batches, it's what is the data. That's the key criteria that you're looking at, and how are you going to analyze that data using what tools. You have two considerations, the product attributes, and you have the process parameters and the ability to control them. So any criteria needs to account for both of those in some cogent, appropriate manner that I really think will differ from product to product and process to process. The agency isn't going to dictate that. As far as number ... there is this element of reproducibility, so right off the bat you know you've got to have more than one. And when I say one I don't mean one batch. I mean, I'd rather say data point, or for whatever the data points that are important or for whatever the attributes or parameters are important, reproducibility is an element that needs to be demonstrated.

Q Why doesn't the guide talk about revalidation?

A We didn't use "revalidation" because really Stage 3, the output of those monitoring activities, is going to give you the impetus to revisit potentially design or revisit Stage 2. So revalidation is really a function of what you find in Stage 3. It's covered in concept, we just didn't use the word. It's something Stage 3 will dictate what you need to do.

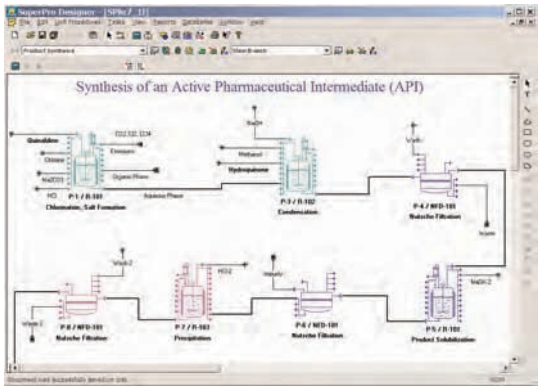
Q Can you please comment on the responsibilities of manufacturers of record and contract manufacturers? Who's responsible for the validation?

A Ultimately the manufacturer or the company's name that's on the label is responsible. Having said that, it's impossible for the contract manufacturer not to be involved. I know that there are these quality agreements that the contract manufacturer and the actual manufacturer of record will negotiate and the responsibilities should be laid out in these quality agreements. So there are special considerations. And that's very prevalent. There are lots of contract manufacturers even within one company so that has to be worked out and transferred, whether to a site in India or in the US... Both parties are going to have some responsibility because they will each be inspected on their own merit; they are registered drug companies. If you're responsible for transfer of a process to another location, that needs to be one of your primary concerns in getting those responsibilities laid out and understood by all parties.

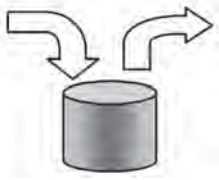
Intelligen Suite

The Market-Leading Engineering Suite for Modeling, Evaluation, Scheduling, and Debottlenecking of Single & Multi-Product Facilities

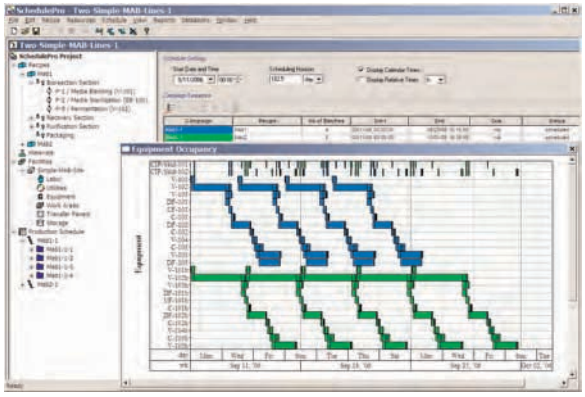
SuperPro



Use SuperPro Designer to model, evaluate, and debottleneck batch and continuous processes

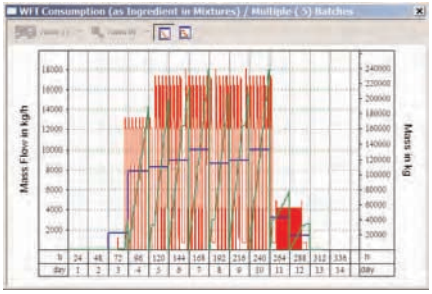


SchedulePro

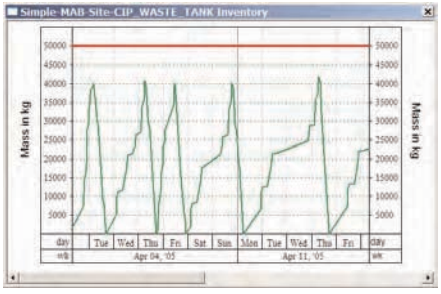


Switch to SchedulePro to schedule, model, and debottleneck multi-product facilities

Tracking of equipment occupancy in multi-product facilities



Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Inventory tracking for raw materials, intermediates, products, and wastes

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of biochemical, specialty chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 400 companies and 500 universities around the world (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile finite capacity scheduling tool that generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of facilities, equipment, resources and work areas. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size utilities for batch plants, identify equipment requirements, reduce cycle times, and debottleneck facilities.

Visit our website to download detailed product literature and functional evaluation versions of our tools

INTELLIGEN, INC. • 2326 Morse Avenue • Scotch Plains, NJ 07076 • USA
Tel: (908) 654-0088 • Fax: (908) 654-3866
Email: info@intelligen.com • Website: www.intelligen.com
Intelligen also has offices in Europe and representatives in countries around the world

This article provides a comparison of the provisions found in ASTM E2500 versus the expectations for equipment qualification as enunciated in the FDA's recent draft process validation guidance.

A Comparison of the FDA's Draft Process Validation Guidance and ASTM E2500

by Robert E. Chew, PE

Introduction

The pharmaceutical/biotechnology industry has shown great interest in the ASTM Standard E2500[1] for the Design, Specification, and Verification of facilities, equipment, and systems. Many companies are attempting to implement this standard. In quite a few instances, organizations responsible for compliance are concerned that this standard represents a significant change from how industry has practiced qualification in the past. There is a further concern regarding terminology (what certain documents need to be called) and the structure of documents with respect to EU regulatory expectations. The FDA's new draft process validation guidance includes expectations for equipment qualification. How do the expectations in this new guidance compare with the approach defined by ASTM E2500, and how can the EU expectations be reconciled with these documents? This article provides an analysis of these provisions and a recommended approach to equipment qualification.

History

ICH Q9, Quality Risk Management, was finalized at Step 4 in November 2005[2] and has been adopted by the Japanese, EU, and US regulators as either guidance or incorporated into regulations. This document provides principles and examples of tools of quality risk management that can be applied to all aspects of pharmaceutical quality, including development, manufacturing, distribution, and the inspection and submission/review processes. One way (out of many) that risk management can be used is to focus the facility and equipment design and operation around risk to the patient. A qualification approach also can make use of quality risk management to focus on those aspects of the facility, equipment, and automation that provide control of risk to the patient, or otherwise help assure manufacture of a quality product.

The EU GMPs Annex 15 on Qualification and Validation, published in 2001, states that "A risk assessment approach should be used to determine the scope and extent of validation." The document then prescribes use of Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) as being precursors to process validation. These terms are defined and general content is specified. These terms and provisions are echoed in the more recent ICH Q7A, GMPs for manufacture of active pharmaceutical ingredients, which has been adopted by the US, EU, and Japanese regulators as either regulation or official guidance.

In July 2007, ASTM E55 committee (which is developing standards related to pharmaceutical manufacturing) issued its Standard E2500 covering the design, specification, verification, and acceptance of facilities, equipment, and associated automation for use in pharmaceutical and biotechnology manufacturing. The purpose of this standard is to describe how to implement the ICH Q9 principles of quality risk management in a controlled and documented manner that meets regulations and demonstrates manufacturing systems are suitable for their intended use.

In November 2008, the FDA issued its draft update to the 1987 Process Validation Guidance. In January, the FDA delivered a webinar on this subject, hosted by ISPE. See related article on page 8 in this issue for a full discussion of the contents of this draft guidance. Industry has been provided with an opportunity to comment

Continued on page 26.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2009,
Vol. 29 No. 3

High performance teams make the difference.

COMMISSIONING AGENTS.

Our teams are recognized industry leaders in developing better methods to meet your business and regulatory demands. When schedule is your problem, we are your solution.

Major services include:

- Commissioning planning equipment start-up, troubleshooting, and field execution; verification and qualification (IQ, OQ, PQ)
- Quality Risk Management (QRM) Implementation and Risk Based Qualification Programs
- Validation – Process, Cleaning, Sterilization, Computer
- Process Improvement Services: Process Analytical Technology (PAT), technology transfer, process improvement studies
- Technical services including design reviews, SOP development, training
- Maintenance program development and implementation
- cGMP Compliance Services – audits, regulatory reviews, improvement projects, submission assistance, comparability protocols

CAI
Commissioning Agents, Inc.

Achieve world class manufacturing.

Call Robert E. Chew, P.E., President
Robert.Chew@CAgents.com
+1.317.710.1530

COMMISSIONINGAGENTS.COM

An Employee-Owned Company

on this draft guidance, and it remains to be seen the degree to which comments and changes will be incorporated into the final guidance.

ISPE has under development a new Baseline® Guide Volume 12: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment, which will provide details on how to implement a program based on ASTM E2500. ISPE also is developing a Good Practice Guide that will provide further options and approaches to qualification, including how to evolve practices based on the original Baseline® Guide Volume 5: Commissioning and Qualification, toward an ASTM E2500-based approach.

Terminology

For many years, a *Qualified* system meant that there existed a QA pre-approved, executed, and QA post-approved set of documents consisting of an IQ and OQ (and in many cases a PQ) protocol. For computer systems, and later most systems, this set of documents was expanded to include user requirements, functional requirements, traceability matrices, etc. The content of these protocols more often than not was dictated by local procedures. It did not matter whether the protocol content actually corresponded to critical aspects of the system or whether the qualification process actually yielded equipment that was fully functional and ready to manufacture quality product. What mattered was whether the local procedure was followed to develop, execute, and approve each protocol. Today, there are projects where money is being wasted and time is being lost as decisions are made to address procedural issues that are oblivious to good engineering and science and the impact on product quality.

This is changing. The most important change is what it means to *Qualify* a manufacturing system. This change began with ISPE's Baseline® Guide Volume 5: Commissioning and Qualification. This Guide defined IQ, OQ, and PQ in terms of "aspects…that can affect product quality." This is a more focused approach than the traditional approach of inspecting and testing against all engineering specifications (which can yield very thick protocols, a measure of success for some). ICH Q7A defines DQ as "verification that the proposed design… is suitable for the intended purpose." ASTM E2500 defines verification as "a systematic approach to verify that manufacturing systems…are fit for intended use…" The FDA's new draft Process Validation guidance states, "activities undertaken to demonstrate that utilities and pieces of equipment are suitable for their intended use and perform properly is referred to as *Qualification.*" The draft guidance also states, "Focusing on qualification efforts without understanding the manufacturing process may not lead to adequate assurance of quality." In short, a *Qualified* system no longer means one with signed off protocols created and executed per a rigid procedure, but rather a system that has been shown to be *suitable for its intended use.*

This use of the term *Qualification* to mean a demonstration of suitability for use is equivalent to how ASTM E2500 uses the term *Verification*. The author believes that the term *Verification* has a more narrow and specific meaning in the medical device and other industries: *Verification* is the act of confirming, through objective evidence, that a particular feature or specification has been met. This definition fits with the use of the term verification in ICH Q7A, in that DQ, IQ, OQ, and PQ are defined in terms of "documented verification that…"

The third related term is *Commissioning*. The FDA draft guidance states, "It is essential that activities performed to assure proper facility design and commissioning precede PQ." Commissioning is widely used in many industries, particularly the construction industry; therefore, it is a definition that is readily understood by many parties and is of benefit to project teams.

For purposes of this article, the following terminology will be invoked. For additional discussion of this choice of definitions, please see related article in the July/August 2008 issue of *Pharmaceutical Engineering.*[3]

Verification – the act of confirming, through objective evidence, that a particular specification has been met.

Commissioning – a well-planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations.

Qualification – a state, or determination, that the equipment has been found to be suitable for its intended use.

Basis for Qualification

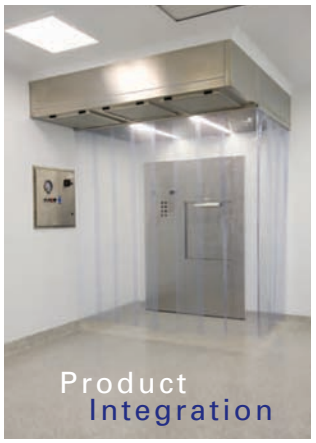
What defines or what constitutes suitability for use? Neither the FDA guidance, nor EU GMPs, address this question in general terms, but instead merely provide examples of qualification activities. See Content and Execution below. ICH Q7A has the general requirement to comply with the approved design and to operate and perform as intended.

The ASTM E2500 standard provides a much clearer definition of what suitability for use is, and how it is assured. While both the FDA draft guidance and the ASTM standard discuss understanding the process science behind manufacturing, the standard goes further to define critical aspects as "functions, features, abilities, and performance characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety." The standard requires the definition of product and process requirements, and the use of risk assessments to identify appropriate controls through design solutions and other means. Collectively, the process requirements and risk assessments can be used to derive the critical design and operating characteristics; these constitute "suitability for use."

The ASTM E2500 standard prescribes a lifecycle approach: "Assurance that manufacturing systems are fit for intended use should not rely solely upon verification after installation, but be achieved by a planned and structured approach applied throughout the system lifecycle." The standard prescribes a series of steps necessary to design, specify, and verify the manufacturing systems. The FDA guidance includes a brief mention of the need to assure proper facility design and commissioning, but does not carry this idea to any greater detail.

Continued on page 28.

A Single Resource...



for TOTAL Cleanroom Confidence.

Planning & executing the right cleanroom solution for your critical process.

AES is your single resource to deliver fast track solutions for Pharma & BIO applications, such as:

- **API Clean Containment**
- **Fill/Finish Processes**
- **Blow/Fill/Seal Facilities**
- **EU/Grade A Laminar Flow Upgrades**
- **Low cost ISO 8/CNC Macro Environments**
- **Cell Manufacturing Facilities**

With the AES Pharma Wall System, combined with our expert knowledge of HVAC and process integration, let us show you how the AES "single resource" team can deliver maximum value to your cleanroom investment.

Call Grant Merrill at 888-237-2532 (ext. 139) to arrange your free consultation today.

aes
Clean Technology, Inc.

1-888-AES-CLEAN ext. 139
237-2532

aesclean.com

The determination, via the ASTM process requirements and risk assessment process, of what constitutes suitability for use is a more robust and process-science driven approach than the FDA guidance "examples." While one cannot argue with the general thrust of these examples, the potential is that industry will focus on these perceived requirements to the detriment of good science and good test engineering practices.

Planning for Qualification

Both the ASTM E2500 standard and the FDA draft guidance are remarkably similar with respect to planning, the only difference being use of *Verification Plan* (ASTM) vs. *Qualification Plan* (FDA). The EU GMPs also contain similar requirements. Table A illustrates the respective requirements for "plans."

Content and Execution

The EU GMPs are the most prescriptive, defining DQ, IQ, OQ, and PQ. Neither the FDA draft guidance nor the ASTM standard defines how the design review and inspection and test programs should be structured; during ISPE's webinar with FDA, the FDA presenter stated that there is no expectation for IQ/OQ/PQ per se. The EU GMPs prescribe content of IQ, OQ, and PQ with IQ having the most prescriptive detail. The FDA draft guidance states, "Qualification of utilities and equipment generally includes the following activities." The examples are similar to the EU content examples and include:

- selection of materials of construction (note the words are selection, not verification!)
- operating principles and performance characteristics appropriate for their specific use
- built and installed per design specifications – and it clarifies this by stating "built as designed with proper materials, capacity, and functions, and properly connected and calibrated."
- Operate in accordance with process requirements in all anticipated operating ranges. This is further amplified to include challenges under load, performance of interventions, start and stoppage as expected during routine operations, and ability to hold operating ranges as long as necessary during routine production operations.

The author feels the above attempts by regulators to engage in the practice of defining the approach and scope of inspections and testing are overly prescriptive. For example, the last sentence regarding the ability to hold operating ranges as long as would be necessary during routine production could lead a team to conclude they have to show the ability to control bioreactor temperature, pH, dissolved oxygen, etc., over a time period equal to a normal cell culture batch, which could be days or weeks. A test engineer would not assess this as being necessary, but would instead understand the science of the process and test those control loops under expected worst case challenge conditions for heat transfer or oxygen uptake, etc. Eventually, of course, such control is by default demonstrated during development batches or process validation lots. However, teams may interpret the guidance regarding qualification of equipment preceding PQ lots as being a hard requirement and endeavor to execute such tests in a non-optimal manner.

The ASTM standard prescribes that specific methods, performance, and documentation of inspection and testing activities are to be determined by subject matter experts. The verification activities should be conducted using a systematic approach and documented, the extent of which is scaled based on risk to patient, risk to product quality, and the complexity and novelty of the equipment. This is a science and risk-based engineering approach. The use of subject matter experts, as defined by the standard, is in complete agreement with 21 CFR 211.25, Personnel Qualifications.

Plan Element	ASTM	FDA	EU
Strategy/studies or tests to use/timing or sequence/scheduling	X	X	X
Define acceptable documentation of detailed activities	X	X	X
QA approval (for systems with critical aspects)	X	X	Note 1
Acceptance criteria	X	X	
Developed and approved by subject matter experts	X		
Responsibilities/organizational structure		X	X
Incorporate risk management to prioritize activities and adjust level of effort in both performance and documentation thereof	X	X	Note 2
Choice to use system-based planning or one overall project plan	X	X	X
Managing change during the project	Note 3	X	X
Validation policy, and reference to existing documents			X
Note 1: Common expectation is that the validation master plan be approved by QA. Note 2: The Principle (preamble) states "A risk assessment approach should be used to determine the scope and extent of validation." It is presumed that the scope and extent are discussed in the validation plan. Note 3: ASTM positions Change Management as a required supporting process to the project, but does not mention it in the context of the verification plan. It is likely teams would choose to include such a subject in their verification plans.			

Table A. Comparison of ASTM, FDA, and EU expectations for contents of a "Qualification Plan (FDA/EU)" or "Verification Plan (ASTM E2500)."

Review, Approval, and Release

ASTM E2500, the EU GMPs, and the FDA draft guidance document all require a summary report following the field inspections and testing. This report is to summarize the findings, highlight any deviations, and describe any changes to the plan/protocol that may have occurred. The ASTM standard describes a two-step process, Verification Review, which is performed by an independent (second check) subject matter expert, followed by an Acceptance and Release, which includes the quality unit for systems with critical aspects. In other words, technical experts review the technical results and make a determination as to suitability for use, while the quality unit provides a final approval of this determination and official release for manufacturing, at which point the system is placed under QA pre-approved change control (vs. change management during the project).

It should be noted that NONE of the three documents describe the typical onerous and formal deviation resolution process present in most projects today. Only the EU GMPs and the ASTM standard mention deviations, and both discuss them in terms of documentation via the final summary report. While the FDA draft guidance does not specifically mention deviations, the subject can be inferred under the contents of the qualification plan: "the criteria appropriate to assess outcomes [should include how to deal with deviations]."

Summary and Recommendations

Table B summarizes the similarities and differences between the US FDA, EU GMPs, and ASTM E2500 with respect to demonstrating manufacturing systems are suitable for their intended use.

It is this author's opinion that if a project team follows the requirements of the ASTM E2500 standard, it will have met the expectations of both US FDA and EU regulators for demonstrating manufacturing system suitability for use. While project teams may choose to be sensitive as to what labels are attached to what documents and to a few particulars of the regulations, overall the ASTM standard provides the most robust, science- and risk-based methodology of any of the documents discussed.

For those who feel more comfortable having documents labeled "DQ, IQ, OQ, and PQ," the following is suggested with respect to documents typically produced during an ASTM E2500-based project.

- The final risk assessment and identification of critical aspects/acceptance criteria and confirmation that the design includes all process requirements could be labeled the DQ.
- A checklist of these critical aspects and their acceptance criteria could be used to review the verification/commissioning work to confirm all critical aspects have been checked.

Concludes on page 30.

Qualification Expectation	ASTM	FDA	EU
Focus on science-based process understanding and meeting process requirements	X	X	
Equipment and facilities suitable for intended use	X	X	
QA approves [qualification] [verification] plan	X	X	
QA approves [qualification] [verification] report	X	X	
QA approves protocols	Note 1	Note 1	Note 2
Risk assessment to "scale" effort, documentation	X	X	X
Flexibility on how effort is structured	X	X	
Specific aspects to check are spelled out		X	X
Critical aspects derived from risk assessments and process requirements	X		
Use of project change management	X	X	X
Use of subject matter experts: how to verify, adjudicate departures from specification	X		
Use of vendor documents	X		
Design and testing of facility, process, equipment based on process understanding	X	X	X
Final report to summarize findings and deviations	X	X	X
Note 1: The QA unit is to approve the acceptance criteria and other high level aspects of the qualification planning effort as discussed under Planning for Qualification. Note 2: QA approval is inferred. EU Annex 15 requires approval of protocols, but does not state by whom.			

Table B. Summary comparison of key expectations of ASTM E2500 program, FDA process validation guidance, and EU GMP Annex 15.

These checklists could be labeled "IQ/OQ" protocols. These checklists could actually be created or copied from the final risk assessment and list of critical aspects, eliminating a separate protocol pre-approval step – the approval of the DQ also could serve as the approval of these checklists.

- A similar approach could be taken for PQ work or a more traditional PQ protocol could be used that includes the specific test cases and instructions for execution.
- These checklists that are labeled IQ/OQ protocols also could be used as the final verification report and the approval thereof would constitute the acceptance and release phase of ASTM standard.

As a cautionary note, it is the author's experience that teams attempting to implement ASTM E2500 with respect to risk assessments and contents of protocols spend significant effort trying to understand and spell out the detailed mechanics of documentation format, structures, what goes where, etc. It also is the author's experience that teams tend to view risk assessments solely through the lens of focusing on the inspection and testing (verification/qualification) effort. That is not the intent of ICH Q9, Quality Risk Management. Instead, it is the author's recommendation that teams approach risk assessments with a holistic view – conduct risk assessments with the idea of identifying, assessing, and controlling risk to the patient through a variety of means (engineering and other quality system-related means). The risk assessments should commence at a high level starting with conceptual design, continuing through more detail as the design develops. It will then become apparent to teams as to how to use these results – to improve the design, to improve procedures, to improve training, to improve other aspects of the quality system, not to mention providing a focus on the critical design and operating aspects of the manufacturing systems.

References

1. ASTM E2500-07: Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment, July 2007.
2. See the FDA/International Conference on Harmonisation (ICH) guidance for industry:
   a. Q8 Pharmaceutical Development
   b. Q9 Quality Risk Management
   c. Q10 Pharmaceutical Quality Systems
3. Adamson, R., Calnan, N., Chew, R., Wisniewski, S., "Commissioning, Qualification, and Verification: A Review Solving the Terminology Conundrum," *Pharmaceutical Engineering*, July/August 2008, Vol. 28 No. 4.

About the Author

Robert E. Chew, PE is President and CEO of Commissioning Agents, Inc. and has 20 years of experience in the pharmaceutical industry. He was a member of the Author Task Team which produced the recent ASTM E2500-07 International Standard. Chew also is a member of the team currently writing the ISPE Baseline Guide Volume 12: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment. He is a former member of ISPE's International Board of Directors, and has been a frequent speaker for ISPE globally. He graduated in 1981 with a BS in chemical engineering from Case Western Reserve University. He can be reached by telephone: +1-317-710-1530 or by email: Robert.Chew@Cagents.com.

Commissioning Agents, Inc. P.O. Box 34320, Indianapolis, Indiana 46234 USA.

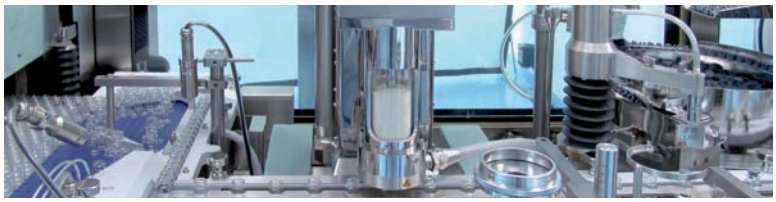
Ad

A compact, clearly structured machine concept for a pharmaceutical company in Austria

Powders today, liquids tomorrow

A multitude of functions for pharmaceutical powders – with the option to fill liquids. And here's the functional process: At first, the glass containers are placed into a washing machine, where they are cleaned and dried. Subsequently, they are hot-air treated in the sterilizing tunnel and later cooled: the cooling zone is sterilizable for this purpose. After the vials are transferred to an interim buffer, they are conveyed to the filling and closing machine in a space-saving solution.

To portion the target weight of 100 mg powder per container with minimum tolerance, the powder dosing requires absolute precision. To achieve such outstanding accuracy, the auger filling system is connected to a 100% in-process-control. An ongoing statistical evaluation of data forms the basis for the tendency control of the doser, so that filling weights are continuously aligned with optimum weight.



Clearly structured design of the line, despite a multitude of functions and lack of space at the customer's site.

Filling is followed by closing – or vacuum drying. Depending on the program pre-selection, either the filling and closing machine places, or inserts plugs within the isolator-protected zone. In the first variant, the containers with the loosely placed plugs are conveyed to an automatic filling and discharge unit feeding the vacuum dryer. The vacuum dryer reduces residual humidity of the filled powder to the defined value.

Following automatic discharge, the vials are closed by a crimping machine processing the bottles independently from height tolerances.

There are no limits to processing liquid sterile pharmaceutical in "parallel" to filling powders, thanks to technology and design. In addition, the vacuum dryer can be upgraded to freeze drying. The concept is transparent and compact, despite its extreme complexity and flexibility – with cameras and sensors, plus a SCADA system additionally ensuring safe machine operation and control.

OPTIMA GROUP

pharma

INOVA
KUGLER
KLEE

OPTIMA GROUP pharma GmbH
Otto-Hahn-Str. 1, 74523 Schwäbisch Hall, Germany
www.optima-group-pharma.com

OPTIMA Machinery Corporation
1330 Contract Drive, Green Bay, WI 54304, USA
www.optima-usa.com

Optima Group is global: In the USA, Mexico, Brazil, France, United Kingdom, Italy, Japan, Korea, China and Germany

Jean-Louis Robert talks candidly about his role with the International Conference on Harmonization (ICH), the continued importance of harmonizing quality standards both within the ICH regions and beyond, and the need for global implementation of initiatives such as Quality by Design (QbD), design space, and risk management.

PHARMACEUTICAL ENGINEERING Interviews

Dr. Jean-Louis Robert, Head of Luxembourg's Laboratoire National de Santé, Service du Contrôle des Medicaments

by Dr. John C. Berridge

The following is a recent interview with Jean-Louis Robert, Head of Luxembourg's Laboratoire National de Santé, Service du Contrôle des Medicaments, conducted by ISPE's European Regulatory Affairs Advisor, who was a European Industry Representative at the International Conference on Harmonisation (ICH) from its inception until 2007.

Dr. Jean-Louis Robert studied chemistry at the University of Basle (CH) and obtained his PhD from there in 1976. He had a post-doctoral training at the Pharmaceutical Institute of the "Eidgenössische Technische Hochschule" (ETH) in Zurich (CH). He spent one year with a pharmaceutical company before joining the National Health Laboratory (LNS) in Luxembourg. In his current position, he is Head of the Department of Control of Medicines, an Official Medicines Control Laboratory (OMCL) at the LNS, member of the European Directorate for the Quality of Medicines OMCL (Council of Europe, Strasbourg) network. He has been a member of the Committee for Human Medicinal Products (CHMP) since 1995 (co-opted since 2004) at the European Medicines Agency (EMEA) in London and Chairman of the CHMP/CVMP Quality Working Party since 1995. Within the International Conference on Harmonization (ICH), he is or was involved in following topics: Validation of Analytical Procedures (Q2), Common Technical Document-Quality, revision of the guidelines on impurities (Q3A and Q3B), Pharmaceutical Development (Q8), Pharmaceutical Quality System (Q10), and currently he is Rapporteur for the implementation of ICH Q8, Q9, Q10. At the European Pharmacopoeia, he is a member of the Commission and of the group of experts 10 B (synthetic products). Currently he chairs the Steering Committee of the Certificate of Suitability of the European Pharmacopoeia. He also serves as a pharmaceutical expert at WHO.

Q Jean-Louis, today you contribute to a wide variety of activities associated with public health protection. For example, you are the quality representative to the EMEA's Committee on Human Medicinal Products (CHMP) and the Chairman of the Quality Working Party (QWP). For many years, you and I worked closely together as members of a variety of ICH Expert Working Groups. Your latest ICH contribution has been the completion of the Annex to ICH Q8 in November 2008. Congratulations! This surely represents the conclusion of another very valuable ICH guideline.

A Yes, thank you. I was very happy to take over the completion of this guideline after you had led the Expert Working Group through to Step 2 in the ICH process. While principles of Quality by Design (QbD) were not totally new in Europe, it is extremely useful to have a guideline such as Q8(R1) to explain an enhanced approach to pharmaceutical development and all the opportunities linked to it.

Q Can you tell me more about your role and responsibilities as Head of the Laboratoire National de Santé, Service du Contrôle des Medicaments in Luxembourg?

A I am responsible for the laboratory which deals primarily in the quality control of the medicines sold in Luxembourg. This monitoring

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2009,
Vol. 29 No. 3

is done in close collaboration with the Division of Pharmacy and Medicines (Luxembourg Inspectorate) at the national level, and they are responsible for the review and approval of human and veterinary dossiers in Europe. The laboratory is also involved in developing methods to characterize the chemical and physical properties of drugs at pharmacopoeial level. The laboratory is a member of the European Official Medicines Control Laboratories (OMCL) network, coordinated by the European Directorate of Quality of Medicines (Council of Europe, Strasbourg). It is also engaged in anti-counterfeiting activities.

Q Please tell me more about the role and responsibilities of an OMCL.

A An OMCL is an official laboratory that supports the regulatory authorities and complements the inspection services in controlling the quality of medicinal products on the market by independent testing. It is an independent laboratory responsible for the quality control of medicines for human and veterinary use in member states of the Convention on the elaboration of the European Pharmacopoeia and the observer states. The Commission of the European communities and the Council of Europe set up the network in May 1994 and the European Secretariat took on this new responsibility. The main purpose of the European network of OMCLs is the mutual recognition of tests carried out at the national level from countries that belong to the European Union and the sharing of expertise, standardization, and international collaboration for the other countries. Among the many things the network does, it has set up a coordinated European approach for the surveillance of marketed products. It is also responsible for the coordination of the official batch release of vaccines, for example.

Q As an EU expert with the EMEA and representative to the CHMP, what are the main areas that you focus on and contribute to?

A At the CHMP level, my main contributions are for the pharmaceutical quality aspects of submissions. I was nominated to the CPMP, as it was then, in January 1995 and became a co-opted member of the CHMP in 2003. The harmonization of quality standards across Europe is the responsibility of the Quality Working Party (QWP). I have chaired the QWP since March 1995. As an EU expert, I support the activities of the European Directorate for the Quality of Medicines (EDQM) European Pharmacopoeia, OMCL network, and represent Europe in the International Conference on Harmonisation (ICH).

Q Tell us more about the role of the QWP and why is it so important to have an organization such as the QWP?

A As Europe continues to grow, it is vitally important to have a coordinating organization that oversees the development, implementation, and application of common standards and quality systems across all the member states. Where we see the need to develop a guideline for industry regarding a quality matter, we address it through a well-documented and rigorous procedure. We actively seek input from industry and other interested parties across the whole of the community and are always willing to hear comments and suggestions on how we can improve quality standards in Europe, and internationally, for the benefit of patients.

The QWP also represents a single source of scientific advice for industry. We hold regular meetings with companies who seek our input as they progress their candidates through the later stages of development.

In addition, the QWP provides a central point of contact and liaison with other regulatory authorities. For example, we recently collaborated with Health Canada in the elaboration of a guideline for inhaled products, and we frequently welcome visitors from the FDA or other agencies to our QWP meetings. For instance, Swissmedic and the European Pharmacopoeia participate as observers to our meeting.

Q What are your current key priorities as Chairman of the QWP? How do you see the role and priorities of QWP changing or developing over the next decade?

A Right now, our priorities can be seen by reviewing the work programmed on our Web site. In the recent past, we have significantly increased our collaboration with the Inspectors' working party where we are planning greater involvement of assessors with inspectors as we review and approve new marketing authorization applications. We work very closely with the Biological Working Party and this has been especially so with the development of the recent ICH guidelines. Looking further into the future, of course we will continue to adapt to new scientific progress and work across Europe to support the training of assessors, where there may be opportunities to work together with organizations such as ISPE. We do also have a very active PAT team, addressing specific issues with regard to PAT, Quality by Design, giving advice to industry on product related issues. This group chaired by Dr. Keith Pugh from MHRA includes experts from QWP, BWP, and GMDP IWP.

Q Tell us more about your role in ICH. I believe you are the longest serving member of the Quality Expert Working Groups?

A With your recent retirement, I think I am now the longest serving member supporting the quality topics! Clearly, my primary role is to represent the EU in this area. I have really enjoyed working for the past 15 years and still enjoy supporting the harmonization of quality standards both within the ICH regions and those observer countries that adopt the ICH guidelines. One of the more demanding roles is that of the rapport. Generally, industry acts as the rapport until a guideline reaches step two, after which the regulatory authority from the same region will take over the responsibility. Personally, I have led the development of the guidelines concerning analytical validation, impurities (revision), pharmaceutical development part of, the quality aspects of the CTD-Q, and currently Q8, Q9, and Q10 IWG.

Q There are many different initiatives (FDA's initiative on Pharmaceutical Quality Systems for the 21st Century, ICH Guidelines, industry association

Concludes on page 34.

initiatives, etc.) that share the same concepts (some of which are not so "new"), such as QbD, design space, risk management, etc. What do you think is the best way forward to facilitate global implementation of those concepts?

A There are probably two ways which we can facilitate the global implementation of these concepts. Starting with ICH Q8, we have been focusing more on creating a higher level of guidance that is less prescriptive than was perhaps the case with earlier guidelines. This means that there then needs to be agreement on interpretation. Since it is industry, not regulatory authorities, that develops new drugs, it is important for industry to develop and share their understanding on the interpretation and implementation of these guidelines. For example, there have been a number of groups that have developed and published case studies and other training materials that support the implementation of these guidelines. The more we can do that and the more that we can jointly collaborate in their development and elaboration, the greater will be the adoption throughout the world. Secondly, we just need to continue the dialogue. No guideline is ever 100% complete. There will always be questions. The recently established Implementation Working Group (IWG) has a role to document and answer these questions and thereby provide a valuable resource to support the global implementation of the ICH quality guidelines.

Q What is your involvement with ISPE?

A I have enjoyed many years of involvement with ISPE. In addition to contributing to meetings and workshops in both Europe and the USA, I participate in the Regulatory Affairs Committee meetings and contribute to the International Leadership Forum, which is where senior regulators from around the world and Industry executives can share issues relating to quality and make proposals for their resolution.

Q In what ways do you believe a global organization such as ISPE can assist regulators, pharmaceutical companies, and individuals in the international arena, especially in global implementation of these many initiatives?

A I think it is the combination of expertise and the global reach of organizations such as ISPE that facilitates global implementation. ISPE, with its Communities of Practice (COPs), Education Committees, Regional Affiliates, and extensive guides and technology based learning, bridges regulators and industry, and is a powerful resource that can assist everyone whatever region they operate in.

Q In your career, what are the most significant issues or changes you have seen in the global pharmaceutical environment and what changes or challenges do you anticipate in the next few years?

A There have been so many. What I am really pleased to see is the move from assuming quality can be controlled by end product testing to the appreciation of the importance of product and process understanding, thereby supporting continual improvement. The size of the application file has increased though! I've also seen a significant drift away from localized European manufacture to globalized outsourcing, and I do have a concern as to whether industry will be able to maintain their quality standards.

Q For our readers who might want to follow in your distinguished footsteps, what education and preparation is needed for a career in a regulatory agency, particularly as a pharmaceutical assessor?

A Of course there are many routes that one can take to become a pharmaceutical assessor. Studying pharmacy is obviously a good route into regulatory activities, but the scientific degrees of chemistry or biology are also appropriate. These days, I would recommend that a period in industry to gain a wide exposure to contemporary pharmaceutical technology is valuable before considering entering a regulatory agency. I started my career with a BSc in chemistry and then did my PhD in Basle. I stayed in Basle to do a post-Doc at the ETH, and then took my first post in industry at Merck in Darmstadt. I then moved to the laboratory in Luxembourg in 1978 and have been there ever since. The most important is not so much what somebody has studied, but to continuously improve one's scientific knowledge and to be open minded.

Q What has been your most fulfilling role in your career?

A I have really enjoyed working in a small agency because it provided me with a diverse range of opportunities, including the chance to review dossiers (first in the BENELUX registration), to work as part of the OMCL network, and to support the European Pharmacopoeia. I have really enjoyed participating in the development of the EMEA, the establishment of the CPMP/CHMP, and the OMCL network. Of course working in the ICH also has been very exciting. Just for the record, I have not missed a single QWP meeting since it was set up!

Q What kinds of activities do you enjoy in your free time?

A I love being with my family. While I used to play football, jog, and play squash, I spend more time now on my bicycle and I really enjoy the wild and rugged scenery of our local Ardennes. I relax by reading -- thrillers, history, and political commentaries.

Q Are there any other comments/last thoughts you would like to convey to our readers?

A Maybe I can finish this interview with a message to my industry friends and colleagues. I think industry needs to be its greatest critic. It really is important for you to do all you can to achieve the greatest understanding of each other and an understanding of the authorities that regulate you. Do what you can to build trust. We, the authorities, welcome open discussions and transparency, and are always willing to receive new ideas and suggestions from you. As you engage in more and more outsourcing, do pay attention to the quality systems throughout the whole of your supply chain to ensure the robust quality and sustainability of all your supplies.

Filling instinct.

The time has come to take control. IMA Life introduces the latest technological breakthrough in sterile filling: XTREMA F2000. High performances, superb flexibility and easy implementation allow you to bring your sterile processing environment in line with your production objectives, adapting to your needs as they evolve.
Industry experience, proven technology, IMA Life expertise: ingredients which make the XTREMA F2000 much more than a machine.

Come face to face with XTREMA F2000 at Achema 2009
www. ima.it/xtrema

ACHEMA 2009 Frankfurt - May 11-15, 2009/ Hall 3.0 - Stand M2-P21

IMA LIFE S.r.l. • *mktg.filling@ima.it* • *www.ima.it*
IMA NORTH AMERICA, INC. • *sales@imausa.net* • *www.imanorthamerica.com*

IMA LIFE
Aseptic Processing & Filling Solutions

VIAL LOADING • WASHING • DEPYROGENATING • FILLING • FREEZE-DRYING • STOPPERING • CAPPING

PQLI® – What is it?

by Dr. John C. Berridge

This article presents the current status of ISPE's PQLI initiative. It details how PQLI will provide the global industry with the tools necessary to implement the ICH quality vision.

Current Status

ISPE launched its Product Quality Lifecycle Implementation (PQLI®) initiative in June 2007 to help industry find practical approaches to the global implementation of recent ICH guidelines. Through PQLI, ISPE is spearheading approaches to assist in the implementation of, in particular, ICH Q8(R1) (Pharmaceutical Development), Q9 (Quality Risk Management), Q10 (Pharmaceutical Quality System) and imminent Q11, and to support the work of the ICH Implementation Working Group. ISPE is working with industry and regulatory leaders worldwide to support pragmatic and practical implementation of the guidelines based on sound scientific, engineering, and business principles. Key goals of PQLI include the provision of a technical framework comprising, for example, explanatory documents and illustrative examples, supporting the implementation of enhanced science- and risk-based approaches to product realization, technology transfer, commercial manufacture, and its continual improvement in both research- and generic-based organizations. PQLI clearly recognizes that there is no one way to implement the ICH guidelines, rather there are many perfectly satisfactory ways to address the concepts that are described. PQLI is therefore developing a variety of tools to communicate science and risk-based processes, and a growing series of publications demonstrates the areas of current activity (see References).

PQLI encompasses the whole of the product

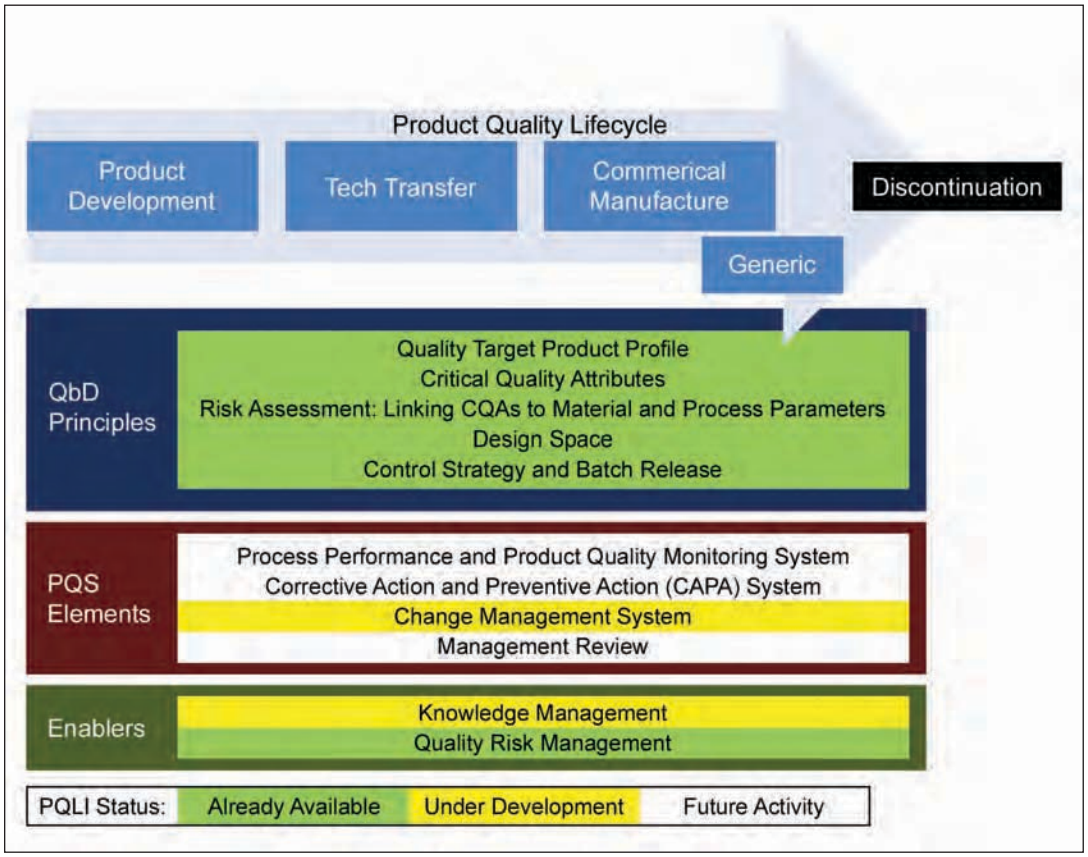


Figure 1. The strategic themes, structure, and status of PQLI.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2009,
Vol. 29 No. 3

"Within PQLI, ISPE has established multi-disciplinary, multi-national teams in support of these strategic themes, addressing them from the perspectives of both small molecules (chemically derived) and biotechnology."

lifecycle and comprises three strategic themes - *Figure 1*.

- Principles of Quality by Design
- Pharmaceutical Quality System Elements
- Enablers

These strategic themes represent the key components of the ICH quality vision described at the July 2003 meeting in Brussels which supported the development of the recent ICH quality guidelines:

> *"Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science."*

Within PQLI, ISPE has established multi-disciplinary, multinational teams in support of these strategic themes, addressing them from the perspectives of both small molecules (chemically derived) and biotechnology. Ensuring alignment with the published ICH guidelines and supporting the future IWG activities is a major focus of PQLI. The PQLI teams benefit enormously though the presence of past and current members of ICH Expert and Implementation working groups and they have further benefitted from input and feedback from members of the three ICH regulatory authorities.

Principles of Quality by Design

The principles of Quality by Design (QbD) are described in ICH Q8(R1). Three multinational, multidisciplinary teams were set up to address the priority topics of Criticality (Critical Quality Attributes and Process Parameters), Design Space, and Control Strategy. Through their deliberations a set of papers was published in the Journal of Pharmaceutical Innovation in June 2008. These papers were published with requests for comments, and from the feedback received it is clear there is a continuing need for PQLI to demonstrate how the concepts of the ICH guidelines translate into practical application in all areas of the product lifecycle. Industry continues to ask to see the high level ICH concepts made simple, real, and practical. A more comprehensive explanatory paper is in preparation to show how the different elements of QbD fit together. Case studies and worked examples are a helpful way of exemplifying the principles and the PQLI teams are actively developing such examples. These examples are all aimed at providing clearer options that demonstrate there are many ways of implementing an enhanced, Quality by Design approach rather than suggesting there is just a single way.

The principles of QbD are applicable throughout the lifecycle, and a publication in JPI (March 2009) describes processes and examples which demonstrate this and show how their application can result in significant business benefits. The paper provides three contrasting case studies which indicate a wealth of opportunities to improve processes for existing products through the use of science- and risk-based approaches, and the subsequent business benefits and regulatory opportunities that can accrue.

The principles of QbD also are equally applicable to biotechnology products. PQLI has an international team of industry experts assembling technical guidance and examples to support this sector of our industry.

Pharmaceutical Quality System

As described in ICH Q10, the opportunities to change the paradigm of development and manufacturing activities for full utilisation of enhanced scientific approaches come only with an integrated and robust pharmaceutical quality system. At our planned conferences in 2009 in Washington, Strasbourg, and San Diego, PQLI is organizing presentations and workshops to

Continued on page 38.

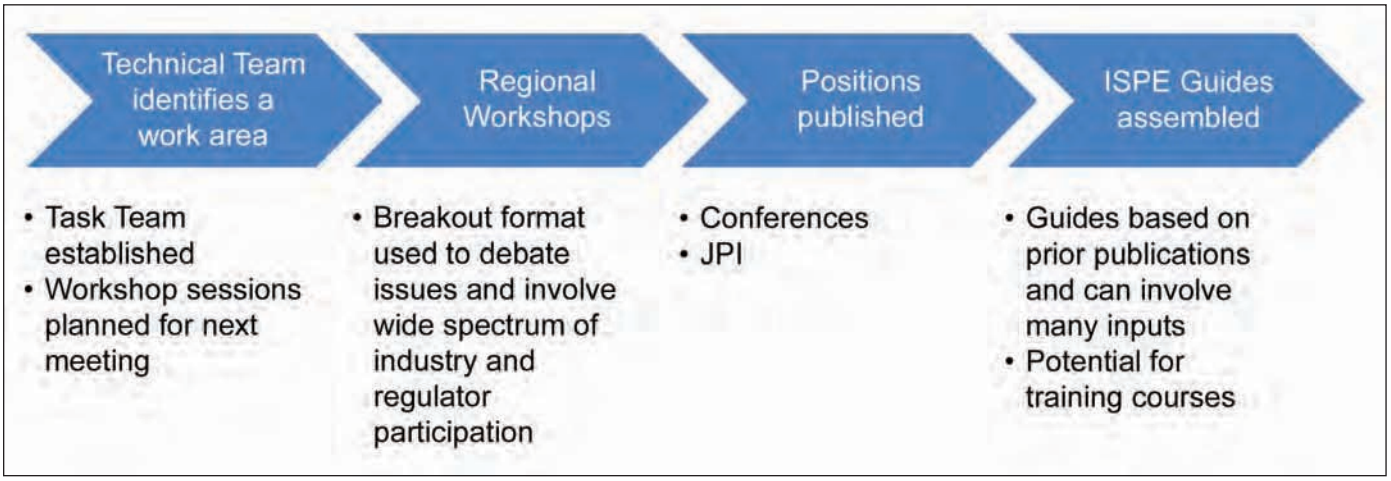


Figure 2. PQLI process to generate technical implementation guidance.

explore the issues and potentially spawn further topic teams to develop the appropriate technical tools.

Enablers

The two enablers described in ICH Q10 are knowledge management and quality risk management. PQLI is addressing quality risk management primarily through the tools being developed to support QbD principles. Knowledge management is a vital enabler that has received little attention so far, but represents the key theme of ISPE's Strasbourg Conference in September 2009 "Managing Knowledge through Science and Risk Assessment."

Future Plans

PQLI will continue its efforts to assist in the adoption and implementation of the ICH quality vision. The goal is to provide a set of resources useful to small, medium, and large innovator companies working on chemical and biotechnology active ingredients and products as well as generic companies. For established concepts, those that are already well-defined by guidelines and the ICH implementation working group, PQLI will continue to support and complement implementation topics with practical case studies, training opportunities and extension of the understanding to global audiences. For example, PQLI has in preparation a technical guide which will describe the continuum of development of a product through to manufacturing and consideration of opportunities for continual improvement. Incorporating the feedback received on the June 2008 JPI papers, it pulls together the foundation work on critical quality attributes and process parameters, design space, and control strategy, linking to many case studies and examples illustrating implementation.

For newer concepts, PQLI will support further debate and discussion through papers, conference presentations, and workshops that involve both industry and regulators: this well established process is illustrated in Figure 2 and is being used to develop implementation guidance around strategic themes 2 and 3.

Conclusions

The vision of the ISPE PQLI initiative is to make available to our global industry the technical and scientific tools and understanding that enable comprehensive implementation of the ICH quality vision. We are fortunate to have on our teams industry experts, current and past members of ICH Expert Working Groups, and to receive excellent feedback from leading regulators across the ICH regions. Building on a foundation of the principles of QbD, PQLI is strengthening this work and now addressing the remaining elements described in ICH Q10 to provide a unique and comprehensive technical framework and set of guides.

ISPE welcomes all contributions, from both members and non-members, who have ideas and examples that describe the practical application of the new ICH quality guidelines. ISPE is keen to collaborate with colleagues and organizations who share the same objectives towards rapid and comprehensive support of the implementation of the ICH quality vision.

If you have any comments, or contributions you wish to make to PQLI, please feel free to email PQLI@ispe.org.

References

PQLI Publications

1. Garcia, T., Cook, G., and Nosal, R., PQLI Key Topics - Criticality, Design Space, and Control Strategy, Journal of Pharmaceutical Innovation (2008) 3:60–68.

2. Nosal, R., and Schultz, T., PQLI Definition of Criticality, Journal of Pharmaceutical Innovation, (2008) 3:69–78.

3. Lepore, J., and Spavins, J., PQLI Design Space, Journal of Pharmaceutical Innovation, (2008) 3:79–87.

4. Davis, B., Lundsberg, L., and Cook, G., PQLI Control Strategy Model and Concepts, Journal of Pharmaceutical Innovation, (2008) 3:95–104.

5. Bolton, R., and Tyler, S., PQLI Engineering Controls and Automation Strategy, Journal of Pharmaceutical Innovation, (2008) 3:88–94.

6. Berridge, J.C., PQLI®: Current Status and Future Plans, Journal of Pharmaceutical Innovation, (2009) 4:1–3.

7. Potter, C., PQLI Application of Science- and Risk-based Approaches (ICH Q8, Q9, and Q10) to Existing Products, Journal of Pharmaceutical Innovation (2009), 4:4–23.

Other Associated or Referring Publications

8. Ende, D., Bronk, K.S., Mustakis, J., O'Connor, G., Santa Maria, C.L., Nosal, R., Watson, T. J. N., API Quality by Design Example from the Torcetrapib Manufacturing Process, Journal of Pharmaceutical Innovation, (2007) 2:71–86.

9. Somma, R., Development Knowledge Can Increase Manufacturing Capability and Facilitate Quality by Design, Journal of Pharmaceutical Innovation, (2007) 2:87–92.

10. Drennen, J.K., III, Editorial: Introducing PQLI Innovations from ISPE's Product Quality Life Cycle Implementation (PQLI) Initiative, Journal of Pharmaceutical Innovation, (2008) 3:59.

11. JPI Interviews Moheb Nasr, PhD, Director, Office of New Drug Quality Assessment (ONDQA), CDER, US FDA, Journal of Pharmaceutical Innovation, (2007) 2:67–70.

About the Author

Dr. John Berridge retired from Pfizer Global Research and Development at Sandwich in January 2006 as Vice President of Pharmaceutical Sciences. He spent more than 31 years at Pfizer, starting as an Analytical Chemist, and more recently responsible for all aspects of chemistry, pharmacy, analytical, and regulatory CMC in Europe. His research interests have been directed toward high performance liquid chromatography with special emphasis on the use of chemometrics. This research was recognized by the award of the Chromatographic Society's Jubilee medal in 1989. Berridge was involved in the ICH processes from their inception until November 2007, representing EFPIA in the Quality topics discussions. He has contributed to guidelines on impurities in drug substances and their dosage forms, specifications, and the Common Technical Document (Quality): he was the Industry rapporteur for the pharmaceutical development guideline (Q8). In 1995, he was presented with an FIP IPS award for his outstanding contribution to industrial pharmacy and in 1997, he was awarded the Royal Pharmaceutical Society Chiroscience award for his services to the pharmaceutical industry. Berridge now acts as an independent consultant and as European Regulatory Affairs Advisor and PQLI project manager to ISPE. He can be contacted by email: pqli@ispe.org.

This article provides a general overview of the organizational structures of the US FDA, EMEA, PIC/S, and ICH as they relate to pharmaceutical manufacturing and regulation. The content in this article is sectioned into three Knowledge Briefs, which are available online and free to ISPE Members.

Global Regulatory Framework Overview: US FDA, EMEA, PIC/S, and ICH

by Dr. Kate McCormick

US FDA

The Food and Drug Administration (FDA) has responsibility for regulation of drugs and biological products which are manufactured and/or sold in the US. The FDA is part of the Health and Human Services Department of the US government. Its role is to guard the welfare of consumers. Full details of the FDA can be found at: www.fda.gov.

The FDA's authority is based upon various laws and statutory documents, as shown in Figure 1. While drugs fall under the Food, Drug, and Cosmetic Act, biological products fall under not only the Food, Drug, and Cosmetic Act, but also the Public Health Service Act.

While the statutes provide the legal basis for the FDA's authority, the regulations which they enforce are contained within the Code of Federal Regulations, Title 21. Of particular importance in relation to manufacturing are parts 210 and 211. These are generally written as 21CFR 210 and 21CFR 211.

Organizational Structure

As Figure 2 shows, the FDA is divided into seven main divisions or Centers. Detailed organization charts can be found at: http://www.fda.gov/oc/orgcharts/orgchart.html.

The Centers and Offices that have particular relevance to the regulation of drugs and biological products are discussed below.

Office of Regulatory Affairs

The Office of Regulatory Affairs (ORA) is the lead office for all field activities of the FDA. The duties and functions of ORA are divided between four main Offices: Resource Management, Regional Operations, Criminal Investigations, and Enforcement. ORA regions are the Pacific, Southwest, Central, Southeast, and Northeast regions of the US. Each region supports a number of local FDA offices.

Center for Biologics Evaluation and Research

The mission of the Center for Biologics Evaluation and Research (CBER) is to protect and enhance public health through the regulation of certain therapeutic biological products as well as blood products, vaccines, and tissue and gene therapy products.

Center for Drug Evaluation and Research

The Center for Drug Evaluation and Research (CDER) is responsible for the regulation of chemically-derived and most therapeutic biological products, both new drugs and generics.

Product Type	FD&C Act	PHS Act	Component Jurisdiction	Generic Equivalence	Establishment Standards	21 CFR Part 211	21 CFR 312	21 CFR 600 ff	21 CFR 314
Drugs	✓		✓	✓		✓	✓		✓
Biological Products	✓	✓	✓		✓	✓	✓	✓	

Figure 1. Statutory and Regulatory Authorities.

Center for Devices and Radiological Health

The Center for Devices and Radiological Health (CDRH) is responsible for the regulation of medical devices and radiation emitting products.

Office of Combination Products

The Office of Combination Products (OCP) is an office within the FDA's Office of the Commissioner, which is

Continued on page 42.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2009,
Vol. 29 No. 3

Innovation
makes it possible

Telstar Life Science solutions is constantly innovating to offer tailor-made solutions in high technology equipment for the pharmaceutical, biotech and related industries.

With over 45 years of experience and an international presence in more than 100 countries, Telstar is your partner to provide solutions in the following technologies:

Telstar ACE

High Containment Isolators

Telstar Celester

Sterilization Systems, WFI & Pharmaceutical Steam Generation Systems

Telstar Lyo

Freeze Drying Systems

Containment Systems
- Isolators
- Restricted Access Barrier Systems (RABS)
- Downflow booths

Sterilization Systems
- Moist heat sterilization autoclaves
- Chemical agent sterilization autoclaves
- Sterilization and depyrogenation ovens

WFI & Pharmaceutical Steam Generation Systems
- Multiple/simple effects stills
- Pure steam generators

Freeze Drying Systems
- GMP production freeze dryers
- Laboratory freeze dryers
- Loading & unloading systems
- Lyophilization supports services

Laminar Air Flow Systems
- Laminar flow benches
- Biosafety cabinets
- Laminar flow booths
- Customized cabinets

Drying Systems
- Hot air drying
- Vacuum drying

Telstar®
Life Science solutions

TELSTAR LIFE SCIENCES
Josep Tapioles 120
08226 Terrassa (Spain)
T. +34 937 361 600
F. +34 937 859 342
sales.pharma@telstar.eu

TELSTAR NORTH AMERICA
1504 Grundy's Lane,
Bristol, PA 19007 (USA)
T. +1 215 826 0770
F. +1 215 826 0222
telstar.na@telstar.eu

www.telstar-lifesciences.com

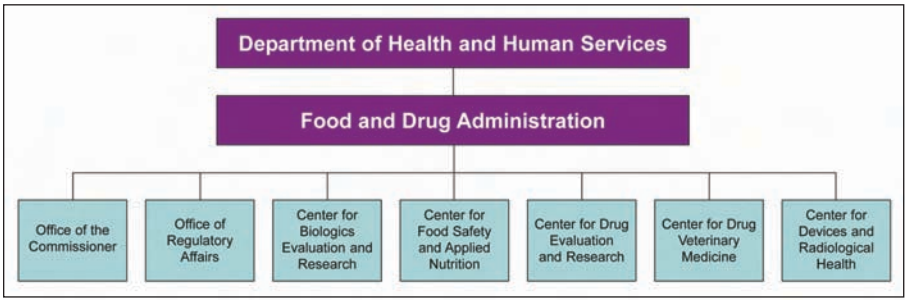


Figure 2. Organizational structure of the FDA.

responsible for general oversight of the agency's regulation of combination products. The primary responsibilities for regulating specific combination products remain in one of the product centers – CDER, CBER, or the CDRH. The OCP is responsible for assigning an FDA center to have primary jurisdiction (lead center) over a particular combination product. The OCP also oversees multi-center reviews of combination products, ensures consistent and appropriate post-approval regulation of combination products, and resolves disputes relating to combination products.

Team Biologics

The FDA Team Biologics was established in 1997 to assure the quality and safety of biological products. It consists of a core team of certified ORA investigators, CBER certified inspectors, and specially trained compliance officers representing both ORA and CBER.

Pharmaceutical Inspectorate

FDA's Pharmaceutical Inspectorate was established under the agency's Pharmaceutical CGMP's for the 21st Century: A Risk-Based Approach. This is a group of certified FDA drug investigators who have received advanced training in drug development, manufacturing, quality assurance, and risk management. These investigators, as well as other FDA drug investigators, inspect all facilities that are regulated by CDER, including those manufacturing therapeutic biological products. The Pharmaceutical Inspectorate is often assigned to inspect the higher risk drug manufacturing facilities.

Licensing/Approval Procedure

Figure 3 shows the approval or licensing process for a New Chemical Entity (NCE) by the FDA. The process, which can take up to 15 years in total, may be divided into 8 phases. Firstly, there is the pre-clinical stage, lasting between 3.5 and 6.5 years. During this stage in-vitro and in-vivo (animal) studies are carried out to assess safety and biological activity. At the conclusion of this stage, the company files an Investigational New Drug (IND) application. In effect, this is a request for a permit for the drug to be transported across state boundaries for the purposes of clinical trials.

Clinical trials are carried out on humans. In Phase I, which lasts up to 1.5 years, the drug is tested on healthy volunteers to prove it is safe and to identify the appropriate dosage.

	Preclinical		Phase I	Phase II	Phase III		FDA		Phase IV
Years	3.5 - 6.5		1 - 1.5	2	3 - 3.5		1.5 - 2.5	15 Total	
Test Population	Laboratory and Animal Studies	File IND with FDA	20 - 80 Healthy Volunteers	100 - 300 Patient Volunteers	1,000 - 3,000 Patient Volunteers	File NDA with FDA			
Purpose	Assess Safety and Biological Activity		Determine Safety and Dosage	Evaluate Effectiveness, Look for Side Effects	Confirm Effectiveness, Monitor Adverse Reactions for Long Term		Review Process/ Approval		Additional Post-Marketing Testing
Success Rate	5,000 Compounds Evaluated			5 enter Clinical Trials			1 Approved		

Figure 3. The FDA approval or licensing process for a New Chemical Entity (NCE).

In Phase II, which lasts 2 years, a small number of patients are voluntarily given the drug to determine its effectiveness and to highlight any side effects.

In Phase III, a much larger population of patients is given the drug to confirm its effectiveness and to identify any adverse reactions over a longer period of time. This phase lasts for between 3 and 3.5 years. Once these phases have been completed, the company files a New Drug Application (NDA) or a Biological Licensing Application (BLA) with the FDA. The process of assessment and approval by the FDA takes between 1.5 and 2.5 years. Once the drug has been approved and is marketed, there is a much larger potential population for further testing. Additional post approval testing related to a drug's approved indication(s) intended to optimize the safe and effective use of the drug is called Phase IV testing.

It can be seen from the bottom of the figure that each approved drug arises from the evaluation of an average of 5,000 compounds.

Pharmaceuticals in the 21st Century

In August 2002, the FDA launched its initiative "Pharmaceutical cGMPs for the 21st Century – A Risk-based Approach." The launch document included the following statement:

"FDA resources will be used most effectively and efficiently to address the most significant health risks."

In other words, the agency does not have sufficient resources to regularly inspect all the sites around the world that are making drugs and biological products for the US market. Hence, it would use risk management to decide the priorities for inspection.

At the same time, it said it required from companies:

"The most up-to-date concepts of risk management and quality systems approaches to be incorporated, while continuing to ensure product quality."

The FDA wants companies to enhance the scientific approach to GMP to emphasize risk-based control point analysis and decision-making. In other

words, for each situation, risks should be assessed as a precursor to deciding what action, and at what level, is appropriate.

While this initiative was launched by the FDA, it is in line with the philosophy of both the EU and Japanese regulators. It is the basis of recent activities within ICH, culminating in the publication of three new guidelines: ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System).

EMEA

The European Medicines Agency (EMEA) (http://www.emea.europa.eu/) has overall responsibility for regulation of medicinal products within the European Union (EU) (http://europa.eu/).

The EU is an expanding group of countries in Europe that have committed to economic and political union. As of 1 January 2009, there are 27 Member States. The current members are shown in Figure 4.

Regulatory Documentation

In terms of regulation of manufacture of medicinal products, all member States are bound by a single set of legislation (Directives) and regulations. In the EU, regulation of medicinal products is the same both for human and veterinary products. However, the legislation is covered by two Directives, both originating from 2001: 2001/83/EC relates to products for human use and, 2001/82/EC relates to veterinary products.

Over time, these Directives have been amended; most recently, they have been expanded to include the manufacture of herbal medicines:

- Directive 2004/27/EC (amending Directive 2001/83/EC on human medicines).
- Directive 2004/28/EC (amending Directive 2001/82/EC on veterinary medicines).

The Directives are expanded and explained via a series of guidance documents.

All these references are contained in "The rules governing medicinal products in the European Community." They are available at: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm.

There are currently 10 volumes covering different aspects of medicinal products from development and registration through to marketing. Volumes 1 and 5 contain all the legislation, including the directives mentioned previously. The remaining volumes contain the guidance documents.

Volume 4 is of specific interest as it concerns good manufacturing practices for medicines. It is divided into two parts: Part I covers the requirements for the manufacture of finished products or secondary manufacturing, as it is sometimes called, and Part II covers the requirements for the manufacture of active substances, also known as Active Pharmaceutical Ingredients (APIs) or sometimes as drug substances.

In addition to Parts I and II, there are a number of annexes. In some cases,

Continued on page 44.

Figure 4. Member states of the European Union (EU) as of 1 January 2009.

these represent the requirements relating to specific types of products, whereas others expand on the requirements of Part I or deal with new concepts that have developed since the main text was published.

The European Medicines Agency

The EMEA was set up in 1995 as the European Agency for the Evaluation of Medicinal Products. It later became known as the European Medicines Evaluation Agency (hence the acronym EMEA), but has since changed its name to the European Medicines Agency.

The EMEA is responsible for evaluation of the safety, efficacy, and quality of products which are submitted for a marketing authorization within the EU. The EMEA:

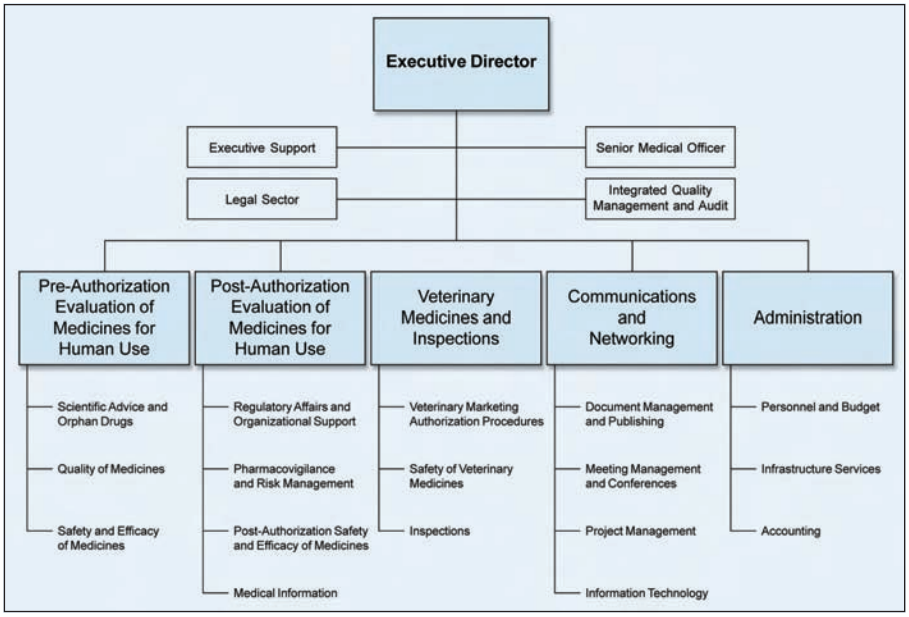


Figure 5. Organizational structure of the EMEA.

- provides independent, science-based recommendations on the quality, safety, and efficacy of medicines and on more general issues relevant to public and animal health that involve medicines.
- applies efficient and transparent evaluation procedures to help bring new medicines to the market by means of a single, EU-wide marketing authorization granted by the European Commission.
- implements measures for continuously supervising the quality, safety, and efficacy of authorized medicines to ensure that their benefits outweigh their risks.
- provides scientific advice and incentives to stimulate the development and improve the availability of innovative new medicines.
- recommends safe limits for residues of veterinary medicines used in food-producing animals for the establishment of maximum residue limits by the European Commission.
- involves representatives of patients, healthcare professionals, and other stakeholders in its work, to facilitate dialogue on issues of common interest.
- publishes impartial and comprehensive information about medicines and their use.
- develops best practice for medicines evaluation and supervision in Europe, and contributes alongside Member States and the European Commission to the harmonization of regulatory standards at the international level.

The EMEA is a scientific body that advises individual Member States and other bodies within the EU and uses a network of scientists from across the EU to facilitate the operation of the evaluation system. It has responsibility for the procedures to authorize pharmaceuticals, monitor them once in the marketplace and withdraw that authorization if there is evidence of a problem. The EMEA also operates information sources and electronic communication in order to enhance the safe use of pharmaceuticals within the EU.

Organizational Structure

The EMEA is located in London. Its organizational structure is shown in Figure 5.

The EMEA is divided into five divisions, three of which involve review and approval responsibilities. One division focuses on pre-authorization (assessment of drugs before they are launched on the market place) while another deals with post-authorization of medicines for human use (evaluation of drugs after they have been launched, primarily through the pharmacovigilance system).

The EMEA inspection section is in the same division as veterinary medicines. However, this is for organizational reasons only; the inspections section relates both to human and veterinary medicines. Communications and administration functions round out the remaining two divisions.

It is important to note that while the EMEA coordinates GMP inspection activities across the Member States, it does not have any inspectors in the section. Each Member State has one or more national inspection bodies responsible for carrying out the inspections. There is mutual recognition of these inspections across all Member States.

Authorization Procedures within the EU

There are a number of different ways in which drugs can be authorized for sale in the EU, depending on the nature of the drug and its supply chain:

Centralized Procedure

For some specific drug types, including biotechnology products, orphan drugs, and veterinary growth enhancers, it is mandatory to use the centralized procedure. A single application is made to the EMEA and authorization, if granted, applies across all Member States.

Mutual Recognition Procedure

For the majority of conventional drugs, the mutual recognition procedure is applicable. As the name suggests, an authorization which has already been granted by one Member State will be recognized by other Member States. In this case, a separate application is required, but a full assessment will not be carried out.

Decentralized Procedure

Under the decentralized procedure, which also is applicable for conventional drugs, an application is made simultaneously to a number of Member States. One State is appointed as the Reference Member State to carry out the assessment. Authorization, if granted, will apply within the States to which the application was made.

National Authorizations

It also is possible for a drug to be registered for sale in a single Member State only. This is particularly used for legacy products that are imported from third countries (countries outside of the EU), where the license was in place before the importing countries had access to the EU.

Continued on page 46.

Summary

The role of regulatory authorities like the European Medicines Agency in the scientific evaluation and oversight of medicines is critical in the assurance of both public and animal health. To learn more about the agency and its operations and purview, please visit their web site: http://www.emea.europa.eu/.

PIC/S and ICH

The evaluation and approval of medicines for human use along with responsibilities for inspection and oversight of the manufacturing and distribution of these medicines occurs at numerous agencies around the globe. Manufacturers of pharmaceutical products face substantial challenges in assuring that their products and processes conform to the varied requirements of these agencies. These organizations are the Pharmaceutical Inspection Co-operation Scheme (PIC/S), which is primarily involved in mutual recognition of GMP inspection results between the regulatory authorities of its members, and the International Conference on Harmonisation (ICH), which is primarily involved in harmonized drug regulatory requirements between Europe, the US, and Japan.

Establishment and Purpose of PIC/S

PIC was set up in 1970 under the auspices of the European Free Trade Association (EFTA). Its full title was "The Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products."

PIC is a legally binding treaty between countries. However, under EU law, it is not permissible for individual Member States to sign treaties with countries outside the EU. Only the European Commission can sign such treaties. However, the European Commission is not a member of PIC. If the work of PIC was not to be lost, a compromise needed to be found.

The PIC Scheme (PIC/S) was set up in 1995. It differs from PIC in that it is an informal agreement between regulatory authorities in Member States and is not legally binding. However, its goals are an extension of those of PIC. The purpose of the PIC scheme is:

- to pursue and strengthen the co-operation established between the participating authorities in the field of inspection and related areas with a view to maintaining their mutual confidence and promoting quality assurance of inspections
- to provide the framework for all necessary exchange of information and experience
- to coordinate mutual training for inspectors and other technical experts in related fields
- to continue common efforts toward the improvement and harmonization of technical standards and procedures regarding the inspection of the manufacture of medicinal products and the testing of medicinal products official control laboratories
- to continue common efforts for the development, harmonization, and maintenance of Good Manufacturing Practice (GMP)
- to extend the cooperation to other competent authorities having the national arrangements necessary to apply equivalent standards and procedures with a view to contributing to global harmonization

The PIC/S Web site, www.picscheme.org, is a very useful reference site.

PIC/S Publications

The documentation that is developed and published by PIC/S is useful both for the inspectorates (for whom the references are primarily intended) and also for industry (who can use the references to understand what inspectors are going to look for).

The GMP guide PE009-7 was issued in its latest form in May 2007. It is virtually identical to the EU Part I document apart from minor changes in terminology and one annex.

Other key guidelines include those relating to blood establishments and APIs. The guideline on Site Master Files includes a template that many companies use to write their own SMF.

These and other publications are available in downloadable PDF formats from the PIC/S web site.

Membership of PIC/S

In order to become a member of PIC/S, the authority in question has to demonstrate that it has the organizational framework and procedures in place to apply a GMP inspection system that is at least on a par with those of the other members. This will include a formal quality management system similar to ISO 9000, although it does not need to be externally accredited. The authority also has to demonstrate that it has trained, competent inspectors who can operate the system effectively.

As part of the accession process (and on an ongoing basis) inspectors take part in multinational inspection teams which provides peer review on their systems and practices.

There are currently 37 regulatory authorities, from 34 countries, that are full members of PIC/S, as shown below. (e.g., the Czech Republic and France have 2 authorities, one dealing with human medicines and the other with veterinary products.) Twenty-two of the 27 member States of the EU are included in this number.

At any time, there also will be other regulatory authorities being assessed for membership or having expressed an interest in the workings of PIC/S.

Although all members of PIC/S have to operate to an equivalent standard,

PIC/S Full Members

Argentina, Australia, Austria, Belgium, Canada, Cyprus, Czech Republic (x2), Denmark, Estonia, Finland, France (x2), Germany (x2), Greece, Hungary, Iceland, Ireland, Israel, Italy, Latvia, Liechtenstein, Malaysia, Malta, Netherlands, Norway, Poland, Portugal, Romania, Singapore, Slovak Republic, South Africa, Spain, Sweden, Switzerland, United Kingdom

PIC/S Partners

European Directorate for the Quality of Medicines and Healthcare (EDQM), European Medicines Agency (EMEA) and UNICEF.

Concludes on page 48.

Pharmaceutical Processing Systems

GEA Pharma Systems supplies the world's pharmaceutical companies with state-of-the-art solutions for the processing of active pharmaceuticals, ranging from the processing of API (Active Pharmaceutical Ingredient) to the production of solid dosage forms and sterile liquids finishing.

The GEA Pharma Systems portfolio of leading industry brands includes:

- Aeromatic– Fielder and Collette granulation/drying systems
- Buck contained materials handling systems
- Courtoy advanced tablet presses
- Niro spray drying technology
- Lyophil freeze drying systems including automatic loading and unloading

The combination of these strong brands with a deep commitment to research and development has resulted in GEA Pharma Systems establishing a leading global market position.

Engineering Excellence.

GEA Pharma Systems

9165 Rumsey Road • Columbia, MD 21045
Tel 410 997 7010 • Fax 410 997 5021
E-mail info@niroinc.com • Website www.niroinc.com

they are not all using the same reference documents. For example, the 22 members that also are Member States of the EU will be using Volume 4 Parts I and II.

Other members, such as Canada and Australia, will have their own national documentation. However, if these documents were examined in detail, it would be very difficult to identify significant differences in the principles being expressed.

Establishment and Purpose of ICH

The full title of ICH is "The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use." ICH was set up in 1990 as a joint forum between regulatory authorities and the pharmaceutical industry, with a focus on harmonizing the procedures used to evaluate the safety, quality, and efficacy of medicines. At that time, companies were experiencing difficulties in submitting dossiers for product licenses in different countries and regions due to differing regulatory expectations.

The purpose of ICH was to identify ways in which greater harmonization could be achieved in the interpretation and application of technical guidelines and requirements for product registration. This would reduce the need for duplicate testing during research and development of new medicines.

The objective was therefore more economical use of resources, and elimination of unnecessary delay in the development and availability of new medicines while maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

Since the emphasis was on products containing new drugs, the scope of the activities was limited to registrations in Western Europe, Japan, and the US, where the majority of new medicines are currently developed.

Work occurs within ICH by means of Expert Working Groups which are appointed to develop guidance on specific topics. In the past few years, the scope of ICH discussions has widened to include not only R&D, but also activities relating to manufacturing.

The ICH Web site can be found at: www.ich.org.

ICH Publications

Unlike PIC/S, publications from ICH are for direct use in industry. Topics are subdivided into four categories:

- Quality topics, relating to chemical and biotechnical active ingredients and to pharmaceutical products
- Safety topics, relating to in vitro and in vivo pre-clinical studies
- Efficacy topics, relating to clinical studies in human subjects
- Multidisciplinary topics, where experts from more than one discipline collaborate in the development of guidelines which do not uniquely fit into one of the above categories

In the first category, Quality topics, a widening of scope has been seen. For example, it was via ICH that the guideline for Active Pharmaceutical Ingredient (API) manufacturing has been formalized, with the publication of ICH Q7 Good Manufacturing Practices for Pharmaceutical Ingredients. This has since been incorporated into the regulatory guidance of the EU, Japan, and the US. More recently, a new ICH Quality Vision was developed which spawned guidelines in support of a greater emphasis on science and risk-based approaches.

Three key documents have been produced to date:

- ICH Q8 (R1) Pharmaceutical Development
- ICH Q9 Quality Risk Management
- ICH Q10 Pharmaceutical Quality System

These publications have been the catalysts in creating a major transformation in the ways in which the industry will be developing, manufacturing, and overseeing the quality of future medicines and related products.

For Further Information

For more detailed and related information, the following ISPE resources are available:

1. Overview of FDA – http://www.ispe.org/cs/explore_by_topic/fda_resources
2. What's New at the FDA – http://www.ispe.org/cs/resourcecenter
3. Recent FDA Slide Presentations – http://www.ispe.org/cs/fda_section/recent_fda_slide_presentations
4. What's New at the EMEA – http://www.ispe.org/cs/resourcecenter
5. Knowledge Briefs: http://www.ispe.org/cs/resource_library_section/knowledge_briefs
   - "Quality by Design," by John Berridge, KB-0001-Jun08.
   - "Risk-Based Approaches to Cross Contamination," by Stephanie Wilkins, KB-0004-Oct08.
6. Product Quality Lifecycle Implementation: http://www.ispe.org/pqli

About the Author

Dr. Kate McCormick of Heathside Information Services Ltd, United Kingdom, is a manufacturing consultant with extensive strategic and operational management experience in the pharmaceutical industry, both in the UK and internationally. She has 10 years of line management and 20 years of internal and external consulting experience. She has worked with multinationals, SMEs, non-governmental organizations and national regulatory authorities in more than 50 countries. She is the author of Quality (a textbook within the Butterworth Heinneman pharmaceutical engineering series) and Manufacturing in the Global Pharmaceuticals Industry, the editor of gmp Review and a regular speaker at international conferences. McCormick gained a degree in biochemistry and a doctorate in microbiology, both at London University. She also has a Masters in Business Administration. She is registered as a senior GMP expert within the EU and is eligible as a QP under the terms of the EU directive. She is currently European Education Advisor for ISPE. She can be contacted by telephone: 44-1626-854611 or by email: kate@heathside.com.

This article presents the final data from a survey conducted on the use of barrier isolators for automated fill/finish operations.

Barrier Isolation History and Trends – 2008 Final Data

by Jack Lysfjord and Michael Porter

As the journey in time of barrier isolation technology went from prototypes in the late 1980s and early 1990s to today, there have been questions regarding the need for benchmarking the usage of barrier isolator technology. Another way to say it is; what is everyone else doing in regard to this technology? This survey presents its history and trends. We have attempted to gather as much information as possible to use as a database; however, we also know that we never achieve perfection with all data. Numbers are as good as the data we get, and they are not absolute. Trends are real and that is what should be used for comparison.

This is the sixth survey on the use of Barrier Isolators for automated fill/finish operations that began in 1998. The surveys have been done only on the even years because of the energy content it requires by both the authors and the users. Manual operations in a glovebox are not considered. It is evident that usage of barrier isolator technology continues to become much more common in the industry.

In the advanced aseptic processing arena a new relative has evolved called a Restricted Access Barrier System (RABS). Surveys for this technology were done in 2005 and 2007 with the 2007 data to be presented in another article to be published.

Table A shows 391 total isolators worldwide for aseptic fill/finish applications (that we know of) in 2008 as well as the progression of number of units since 1998. Tables B to D show the major pharmaceutical region breakouts for Asia, Europe, and North America. Figure 1 shows the global deliveries by year. Figures 2 to 4 again show deliveries by year for the three regions.

Some companies embrace technology while others wait. Figure 5 shows companies who have most aggressively embraced the use of isolators. Figures 6 to 8 show the regional breakout information. Table E displays the increasing number of pharmaceutical companies using isolators (99).

1998	2000	2002	2004	2006	2008
84	172	199	256	304	391

Table A. Filling barrier isolators (worldwide).

1998	2000	2002	2004	2006	2008
11	19	30	42	50	59

Table B. Filling barrier isolators (Asia only).

1998	2000	2002	2004	2006	2008
57	85	97	116	146	196

Table C. Filling barrier isolators (Europe only).

1998	2000	2002	2004	2006	2008
35	49	66	90	105	133

Table D. Filling barrier isolators (North America only).

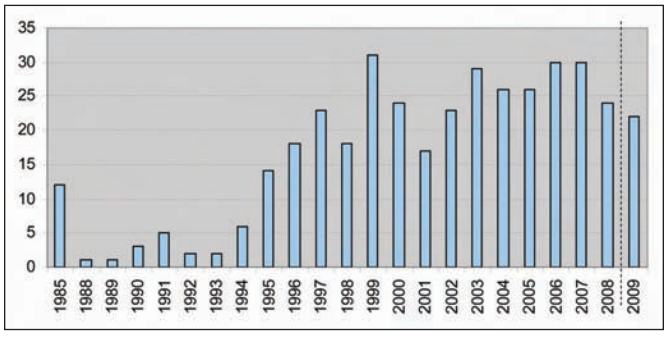


Figure 1. Barrier isolator filling lines – deliveries by year.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2009,
Vol. 29 No. 3

Container type is shown in Figures 9 to 12. It is interesting to see how, for example, the usage of ampoules and syringes in Asia and in Europe compare to in North America.

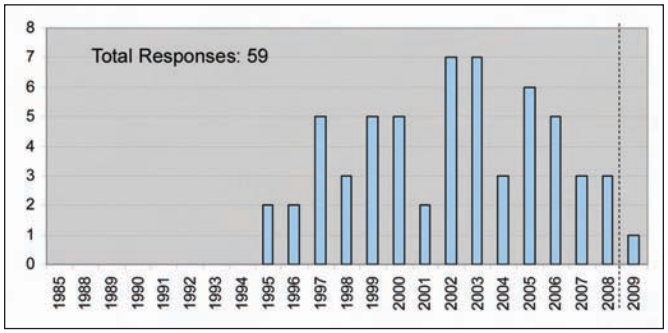


Figure 2. Barrier isolator filling lines – deliveries by year (Asia only).

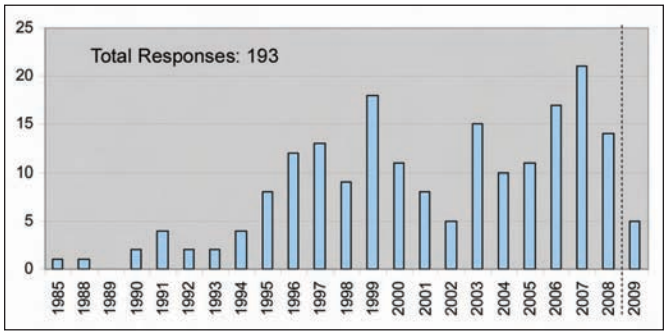


Figure 3. Barrier isolator filling lines – deliveries by year (Europe only).

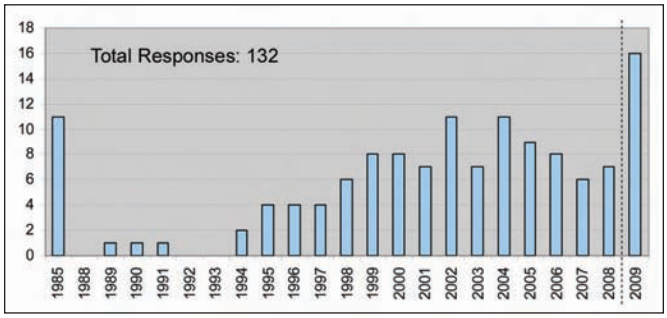


Figure 4. Barrier isolator filling lines – deliveries by year (North America only).

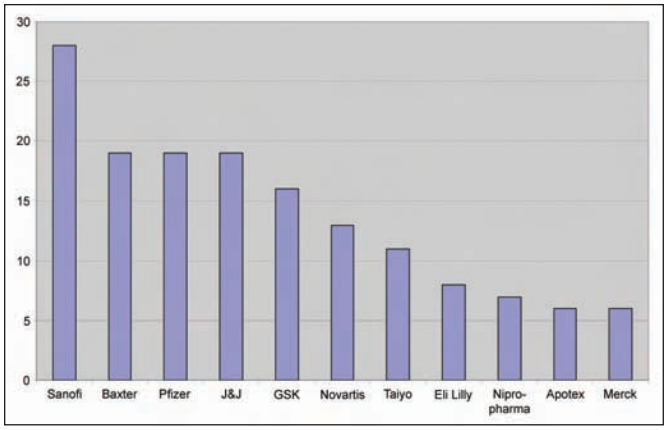


Figure 5. Barrier isolator filling lines – companies with highest usage.

Continued on page 52.

Maximum line speed is shown in the next four graphs 13 to 16. It is interesting to note the majority of isolator usage in North America is for slow speed operation 1 to 100/minute.

Since 1998, the isolators have been hard wall (stainless steel and glass). Soft wall applications were used when the technology started, but reliability, pressure change issues, sterilant absorption, and outgassing pushed the manufacturing to hard wall design.

Surrounding room classification is predominately (65%) ISO 8 in operation with hydrogen peroxide vapor used in 87% of the reported applications for the biodecontamination agent.

Gloves can be one of the most scrutinized areas by regulators. Type of glove used is a decision to be made by users of the technology. Two piece gloves were preferred by 54% over one piece gloves 46%. If gloves are two piece, smooth sleeves are preferred by 86% over pleated sleeves 14%.

Glove replacement period data is in Figure 17 with some

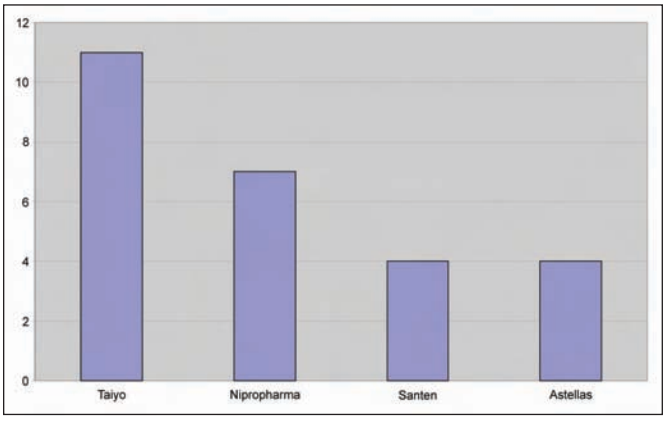


Figure 6. Barrier isolator filling lines – companies with highest usage (Asia only).

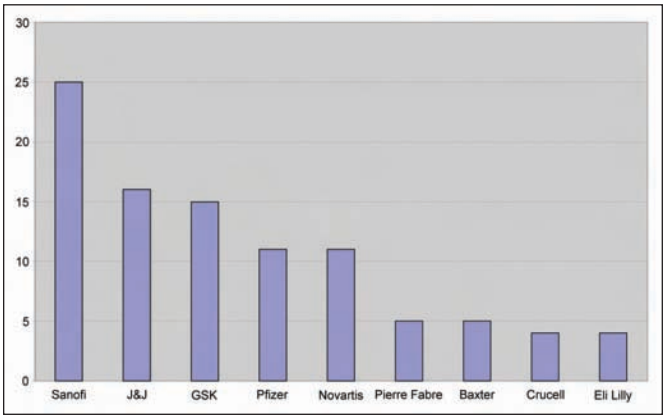


Figure 7. Barrier isolator filling lines – companies with highest usage (Europe only).

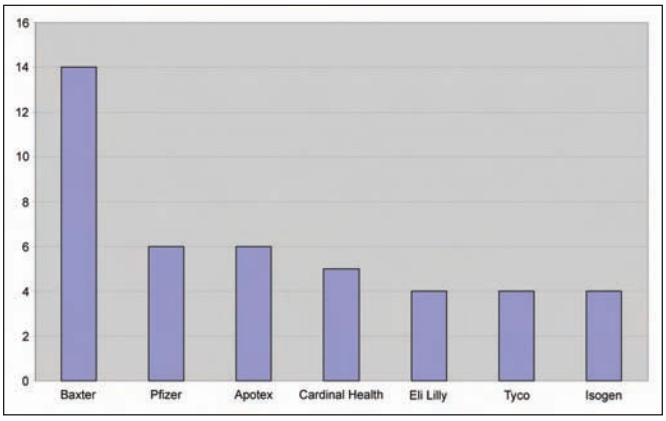


Figure 8. Barrier isolator filling lines – companies with highest usage (North America only).

1998	2000	2002	2004	2006	2008
32	56	67	83	84	99

Table E. Number of companies using barrier isolation.

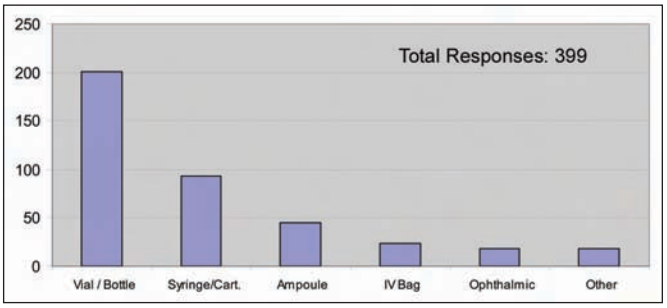


Figure 9. Container type.

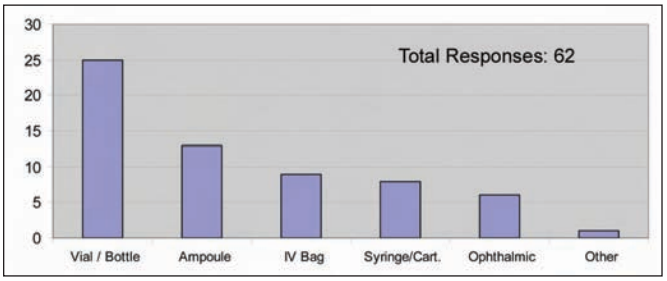


Figure 10. Container type (Asia only).

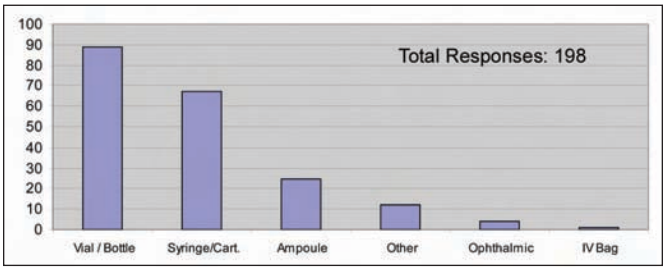


Figure 11. Container type (Europe only).

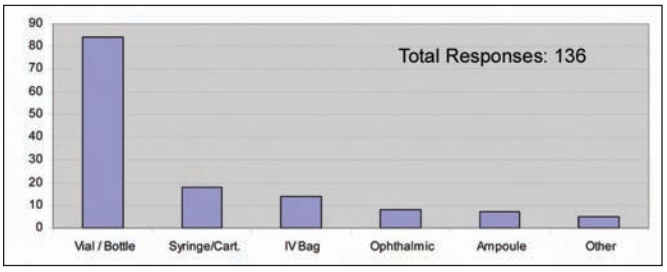


Figure 12. Container type (North America only).

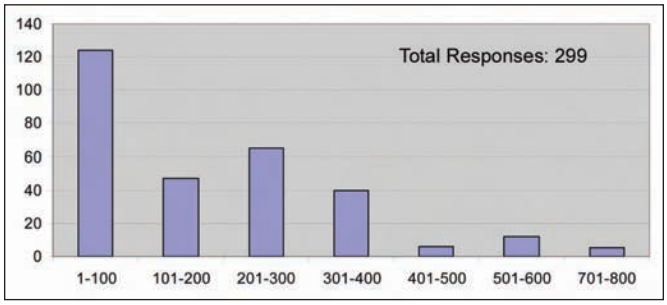


Figure 13. Maximum speed.

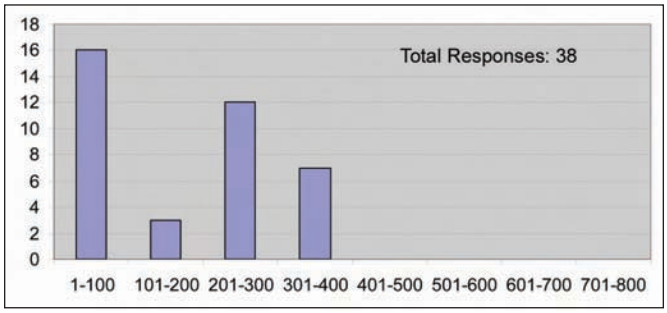


Figure 14. Maximum speed (Asia only).

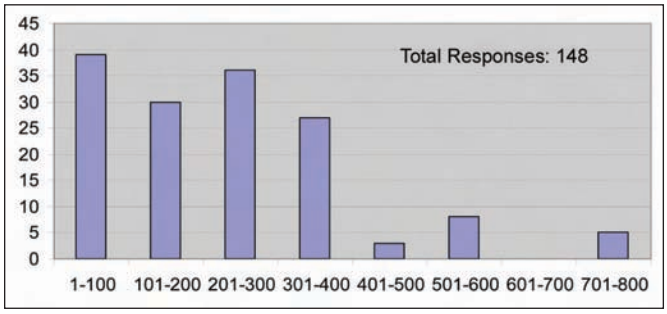


Figure 15. Maximum speed (Europe only).

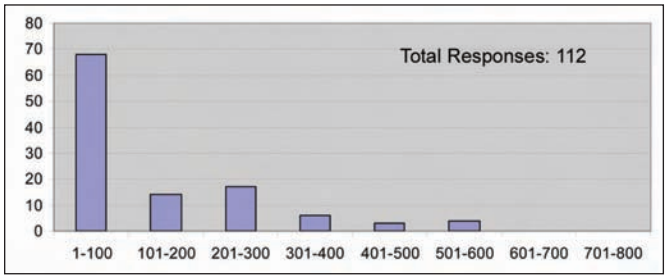


Figure 16. Maximum speed (North America only).

companies able to use gloves up to six months. Method of integrity testing gloves is shown to be predominantly by pressure decay - *Figure 18*. Visual inspection also should be done. 89% of responses indicated usage of a second thin glove with the glove port (typically placed on the hand prior to entering the glove port).

Continued on page 54.

Positive overpressure is typically used in these applications. The concept of "more is always better" does not apply to systems with mouse holes at exits or depyrogenation tunnels that are interfaced with the isolator. Too much overpressure can "blow" the tunnel hot zone air into the washer and melt many parts. Small vials can be blown out of mouse holes destroying the product. Figure 19 indicates that the majority of applications operate between 21 and 40 pascals or ~.1 to .2 inches of water over pressure.

Tunnel sterilizable cool zone technology was used by 65% of those responding.

Containment was a requirement on 42% of total responses over the six surveys. The data with this question must be looked at on a survey by survey basis to look at percent of containment needed on these responses for a two year period. Since 2006, **100%** of 2008 responses indicated a containment need.

Those that indicated that they campaigned product fills within one isolator sterilization event made up 59% of responses. Figure 20 shows the length of campaign from the responses. The maximum campaign length is 28 days.

Finally, cumulative deliveries of isolators are shown in Figure 21. We believe that isolator usage is increasing even faster than shown at the time of writing this article based on equipment manufacturers comments. Data was gathered in first quarter 2008 and the 2009 increase will be much larger than shown here. 2009 data counted was only for what was ordered by first quarter 2008 for delivery in 2009. Many more lines were ordered for 2009 after the data was collected. The dotted line indicates a change in slope after 2004.

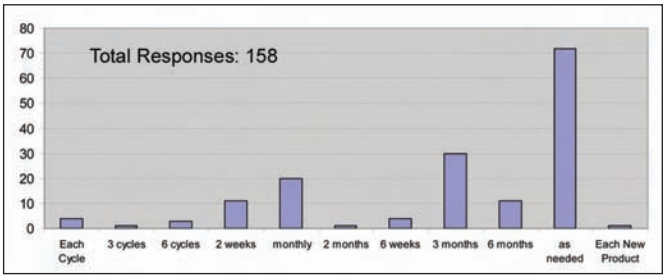


Figure 17. Glove replacement period.

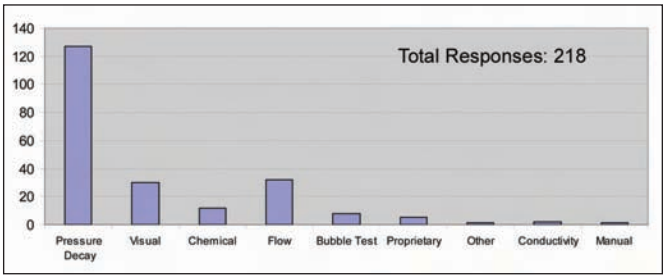


Figure 18. Method for integrity testing of gloves.

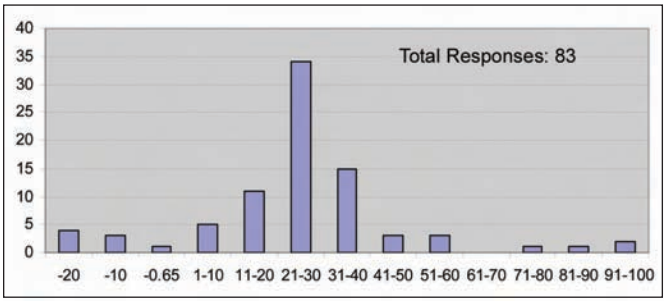


Figure 19. Pressure to washer rooms (12.5 Pascals = .05" Water).

The Trends and Conclusions are:

- Worldwide increase in filling line isolators continues (391) with significant increase in Europe (50) from 2006.
- Asia (9) and North America (28) showed growth in two years.
- Isolators are embraced by some companies and avoided by others.
- Mergers and facility consolidation impact the number of user companies.
- Number of reported isolator lines in operation increased (230 to 283) in two years.
- Vials continue to be the predominant container.
- Hard wall isolators continue to be the preference.
- Smooth sleeve gloves are even stronger than in 2006 (86%).
- Slight preference for two piece gloves (54%).
- Use of a thin second glove is very strong (89%).
- Use of depyrogenation tunnels with sterilizable cool zone increased (65%).

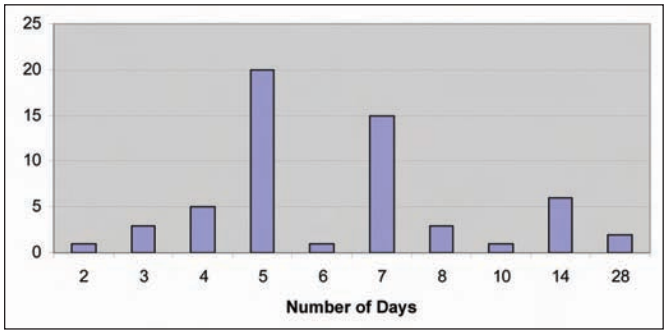


Figure 20. Campaign products (longest run).

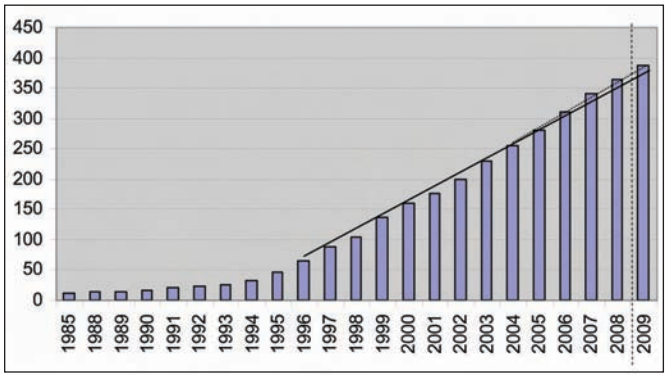


Figure 21. Barrier isolator filling line – cumulative deliveries (2009 is partial data).

- Containment need is increasing (42%) (100% in last two years).
- Campaigning is increasing (59%).

Benchmarking information for those companies investigating the use of isolators is shown below (strongest preferences from survey):

- hard wall isolator; stainless steel and glass
- biodecontamination technology using hydrogen peroxide vapor
- ISO 8 in operation surrounding room classification
- gloves only, meaning minimize use of half-suits for interventions
- two piece gloves with smooth sleeves
- use of a thin second glove
- doing glove integrity tests with pressure decay test (plus visual)

Capital equipment technology and the accompanying depreciation expense last a long time. Remember that today's decisions will impact the company for 15 to 25 years. Look at what is in the pipeline for R&D to make a decision that will cover future products. Many product candidates will have the need of aseptic processing and containment in order to protect both operators and product.

* The author may be contacted for questions or comments by telephone: +1-952-546-2082 or by email: jlysfjord@Q.com.

This article presents the 2007 final data of a survey conducted on the use of RABS for automated fill/finish operations for aseptically filled injectable drugs.

Restricted Access Barrier System (RABS) History and Trends – 2007 Final Data

by Jack Lysfjord and Michael Porter

The authors have done surveys on the use of barrier isolator technology in 1998, 2000, 2002, 2004, and in 2006. These surveys are an attempt to "benchmark" the pharmaceutical industry on a global basis and to look at the historical data and the trends. The data is for automated fill/finish operations for aseptically filled injectable drugs. Manual operations and hand filling and closing in a glove box are not considered. In 2004, a question was asked if it would be possible to get the same type of information for RABS since there seemed to be a great deal of interest in this technology. Due to the energy required to do each survey, the best fit was on the alternate years 2005 and 2007. The 2004 isolator and 2005 surveys were presented in conferences, but not published. The 2005 RABS data points are presented here along with the RABS data from 2007.

RABS is a spin off from isolators. Pfizer, Kalamazoo Michigan (previously Upjohn) in 1992 coined the term RABS for "Restricted Access Barrier System." Their goal was to reduce the contamination risk to a product when filled in a conventional cleanroom situation using existing process equipment. The solution was to create a hard wall barrier with glove ports and transfer ports for stoppers to separate the operator from the critical zone or filling closing zone. This barrier sat in a cleanroom which was class 100 (ISO 5) in operation with full ceiling HEPA filters that generated unidirectional airflow on both the outside and inside of the barrier. The top of the barrier was approximately six inches below the HEPA filters and extended below the filling stoppering machine table top with a three inch air gap to the table top for air to flow out of the barrier with no pressure differential. The doors were physically locked to prevent any interventions. The operator to product separation was by a hard wall barrier together with air flow with no pressure differential – the first RABS.

Isolators provide separation between the operator and product with a hard wall barrier and pressure differential.

The first RABS was a "Passive RABS." There also is "Active RABS" and "Closed RABS" today. Figures 1 to 3 depict types of RABS.

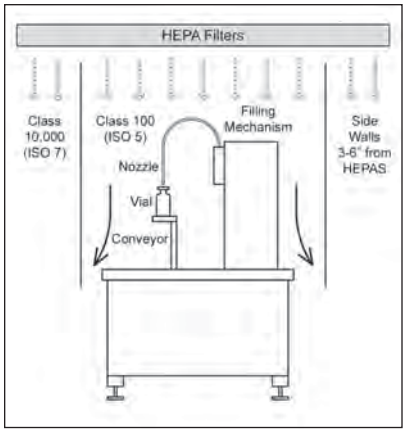


Figure 1. Passive RABS.

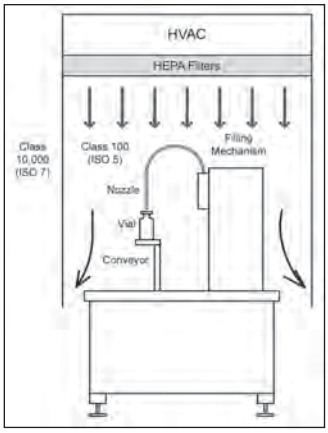


Figure 2. Active RABS.

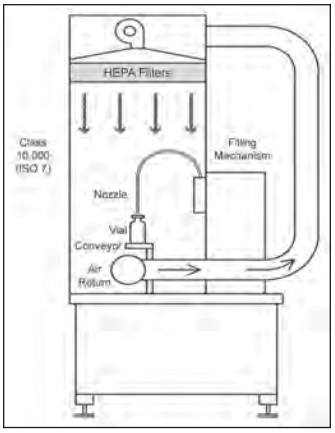


Figure 3. Closed RABS.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2009,
Vol. 29 No. 3

The use of a RABS implies more than the enclosure since the following must be in place for the concept of separation with air flow to be successful and reduce the contamination risk to the product:

- properly designed equipment
- management oversight
- a quality system
- proper surrounding room design (ISO 7 minimum)
  - ISO 5 annex for open door interventions
- proper gowning
- proper cGMP training
- initial high level disinfection with a sporicidal agent
- proper SOP for **rare** allowed interventions
  - disinfection (non sporicidal)
  - line clearance
  - documentation of the event

Year	Asia	Europe	North America	TOTAL
2005	12	40	23	75
2007	23	63	38	124

Table A. Number of RABS units.

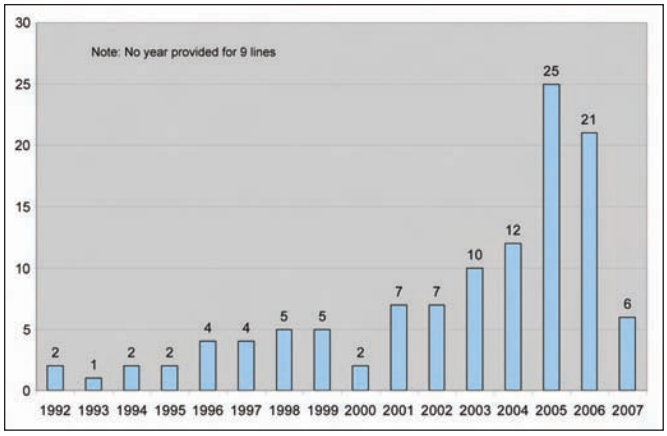


Figure 4. Number of RABS units delivered by year.

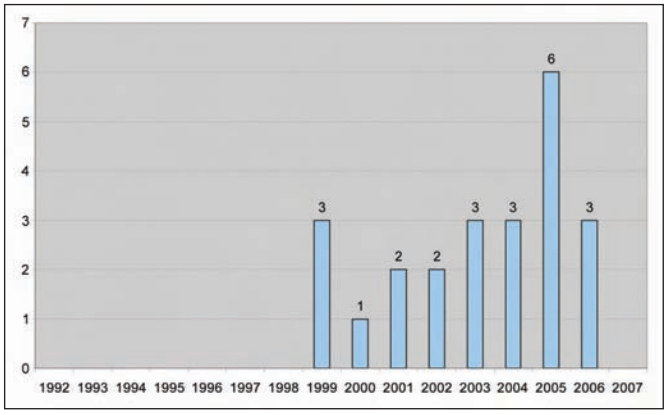


Figure 5. Number of RABS units delivered by year (Asia only).

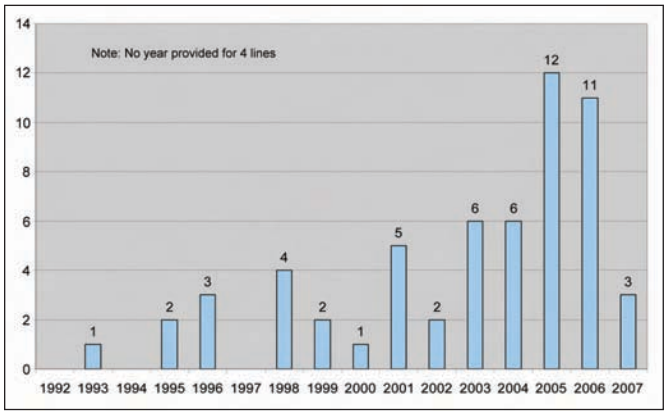


Figure 6. Number of RABS units delivered by year (Europe only).

The S in RABS is for "SYSTEM" and without the systems and procedures above, a simple enclosure is not a RABS and can result in increasing the risk to the product.

In 2005, Stewart Davenport from Pfizer, Kalamazoo, Michigan (part of the team that developed the first RABS) and Joerg Zimmermann from Vetter, Ravensburg, Germany, presented data on cumulative RABS lines media fills from both companies. Each had media fill data that were over one million media fills with no unexplainable positives. They both use the philosophy of never opening the doors of their RABS yielding data equivalent to media fill data of isolators. That is impressive. Here is the survey of RABS history and trends for 2007.

We found 124 RABS in the 2007 RABS survey. Table A gives 2005 and 2007 data and the breakout between Asia, Europe, and North America.

Continued on page 58.

The number of RABS delivered by year overall and the three region breakout are shown in Figures 4 to 7. The types of RABS, passive, active, and closed, are described in Table B. RABS operating philosophy- never opened, limited open, and frequent open responses are shown in Table C. The alarming piece of data indicates many systems (17 companies) frequently open the doors of their RABS.

A listing of the companies with the highest RABS usage is shown in Table D. In 2005, 28 companies had RABS. In 2007, the number increased to 36. In 2005, 25 RABS lines were reported in operation. 36 were in operation in 2007.

Table E shows the RABS lines and the container types that

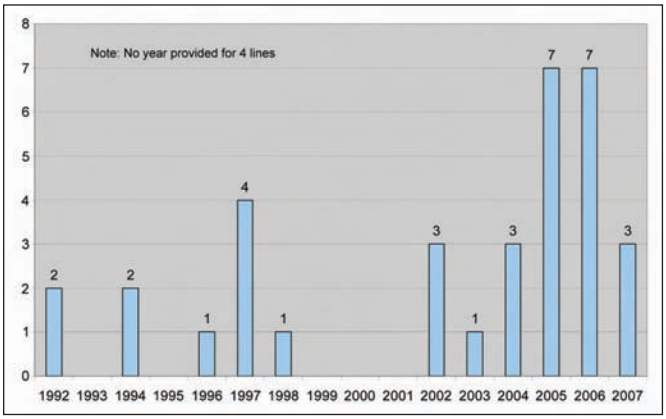


Figure 7. Number of RABS units delivered by year (North America only).

Year	Passive	Active	Closed	TOTAL
2005	16	25	17	58
2007	35	52	39	126

Table B. Types of RABS.

Year	Never Opened	Limited Open	Frequently Open	TOTAL
2005	22	29	1	52
2007	31	48	**17**	96

Table C. Philosophy for using RABS.

	2005		2007	
#	Company	# of Rabs	Company	# of Rabs
1	Vetter Pharma	10	Vetter Pharma	10
2	Pfizer	7	Pfizer	10
3	Aventis	5	GSK	7
4	GSK	4	Aventis	5

Table D. Top 4 companies with RABS.

	2005	2007
Vial/Bottle	48	77
Ampoule	8	12
Syringe/Cartridge	18	29
Ophthalmic	2	5
IV	0	0
Other (including BFS)	0	2
TOTAL Responses	**76**	**125**

Table E. Types of containers processed in RABS.

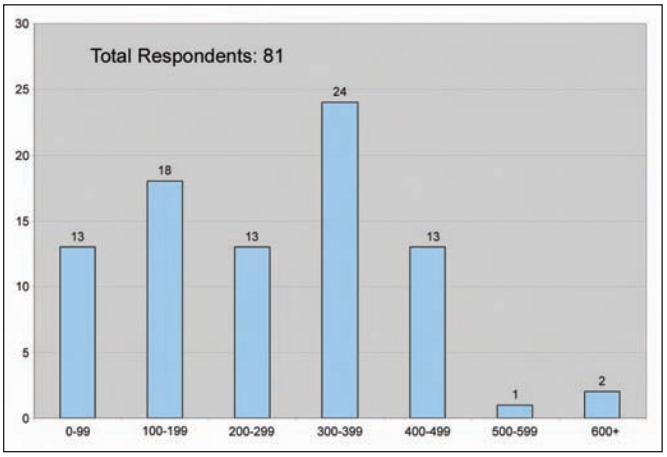


Figure 8. Maximum line speed/minute.

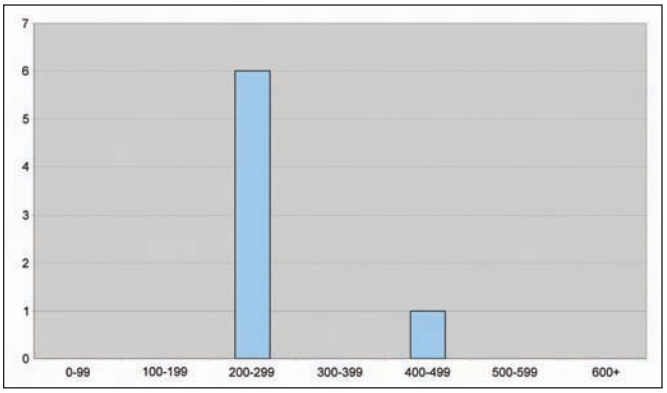


Figure 9. Maximum line speed/minute (Asia only).

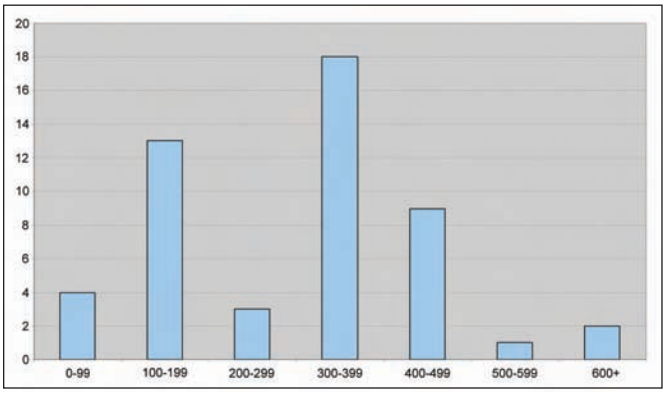


Figure 10. Maximum line speed/minute (Europe only).

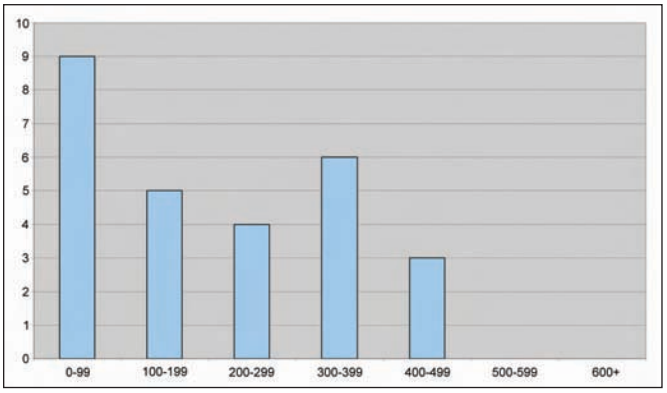


Figure 11. Maximum line speed/minute (North America only).

Year	Autoclave	Sanitize in Place	Other	TOTAL
2005	16	11	4	31
2007	16	21	12	49

Table F. Method of sanitizing gloves.

Year	Yes	No	TOTAL Respondents
2005	29	0	29
2007	31	7	38

Table G. Second inner glove used.

	2005	2007
Each Cycle	4	3
Every 5 Runs	1	1
Every 15 Cycles	10	10
Every 6 Weeks	1	1
Every 3 Months	4	4
Every 6 Months	0	1
As Needed	8	18
TOTAL Responses	**28**	**38**

Table H. Glove replacement time.

	2005	2007
Pressure Decay	20	20
Visual	4	18
Other	2	2
None	1	1
TOTAL Responses	**27**	**41**

Table I. Glove test method.

	2005	2007
Active Oxygen Agent		10
Gas Formaldelhyde		10
Spor Klenz	0	6
Chemical Agent and Formaldehyde Gas	5	5
Peracetic Acids	3	3
Chemica Agent and VHP Gas	2	2
Decon Quat 100	2	2
Germex B12, Apesin AP3, Apesin Rapid	2	2
IPA		2
Rotating Disinfectant Regime		2
2 Phenols + IPA	1	1
Bleach/Detergent		1
Disinfectant Medium Level		
Alkalidetergent High Level		1
Hydrogen Peroxide	1	1
Hypochlorite 5%	2	1
Liquid Disinfectant	1	1
Same as Room Sanitizers, typical		1
Vesphene, LPH	1	1
VHP Gas	1	1
Alcohol 70%, decon. clean	1	
TOTAL Responses	**28**	**38**

Table J. Types of sanitizing agents.

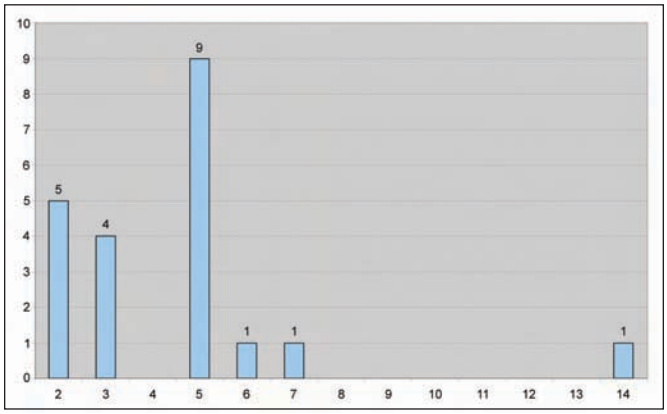


Figure 12. Number of days line campaigned.

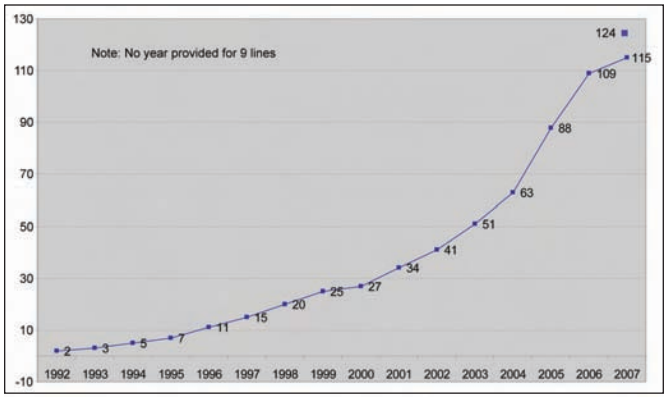


Figure 13. RABS.

they process. Figure 8, 9, 10, and 11 lists frequency of RABS use by maximum line speed in total and then breakouts for the three regions.

Glove data is listed in Tables F, G, H, and I. The types of sanitizing agents used are listed in Table J.

When RABS lines campaign product, the length of campaign in days and frequency are displayed in Figure 12. Six of the responses indicated a need for containment of potent product to protect the operator.

Figure 13 displays the cumulative use of RABS and how the rate of delivery has jumped since 2003. Note that nine responses did not indicate year of delivery to get total to 124 units. In summary:

- RABS use is increasing globally.
- Europe is ahead of North America-similar to isolator data.
- Asia started later, but is increasing in use of RABS.
- RABS is an option to consider to improve asepsis particularly with retrofits.
- Frequent opening of doors on the barrier is a big caution area since it will compromise asepsis. If this is the routine mode of operation, it is not a RABS.

* The author may be contacted for questions or comments by telephone: +1-952-546-2082 or by email: jlysfjord@Q.com.

ENGINEERING PHARMACEUTICAL INNOVATION ISPE

Reprinted from PHARMACEUTICAL ENGINEERING® The Official Magazine of ISPE May/June 2009, Vol. 29 No. 3

US FDA Speakers Figure Prominently at ISPE's 2009 Washington Conference

Numerous regulators from the US Food and Drug Administration (US FDA) were featured speakers at the ISPE 2009 Washington Conference – Engineering Regulatory Compliance, that took place at the JW Marriott in Washington, DC, USA, 1 to 4 June 2009.

Speaker information – along with seminar agendas and training course outlines – for the four-day event are available on the ISPE Web site and include the following listings:

- Richard Friedman (Director, Mfg. and Product Quality, CDER), Tara Gooen (Chemical Engineer, CDER), Robert Sausville (Supervisory Consumer Safety Officer, CBER), and Joyce Rockwell (Consumer Safety Officer, CBER) were featured US FDA speakers at the 18th Annual Barrier Isolation Technology Forum: Innovation Updates and New Case Studies.

- Helen Winkle (Director, Office of Pharmacy, CDER), Christine Moore (Deputy Director, CDER), and Sharmista Chatterjee (Staff Fellow/Reviewer, CDER) were featured US FDA speakers at the PQLI®: Science, Regulatory, Manufacturing, and Engineering Working Together for Global Realization and Implementation of the ICH Quality Vision seminar. Joseph Famulare (Deputy Director, Office of Compliance, CDER), Richard Friedman (Director, Mfg. and Product Quality, CDER), Vibhakar Shah (Consumer Safety Officer, CDER), Elaine Morefield (Supervisory Chemist, CDER), Grace McNally (Senior Compliance Officer, CDER) and Patrick Swann (Deputy Director, Division of Monoclonal Antibody, CDER) of the US FDA were invited, as well.

- Ilisa Bernstein (Sr. Advisor Pharmacist, CDER) and Steven Silverman (Regulatory Counsel, CDER) were featured US FDA speakers at the Global Supply Chain Integrity and Anti-Counterfeiting seminar. A representative from the FDA's Office of Policy and Program Planning, CDER also was invited to speak.

- Barry Rothman, Consumer Safety Officer for the FDA's Division of Manufacturing and Product Quality, CDER was invited to speak at the Current and Future Packaging Challenges for Investigational Products seminar.

- H. Gregg Claycamp, PhD, the Associate Director of Risk Analysis and Strategic Policy Assessment, CVM was the featured FDA speaker at the Applied Risk Management – Addressing Cross Industry Challenges seminar.

- Malcolm Oliver, GMP Inspector for the MHRA, was invited to speak at the Commissioning and Qualification (C&Q): Practical Applications of Science and Risk-based Approaches to Validation seminar, along with several confirmed leaders of the pharmaceutical manufacturing industry.

- As an additional resource on the topic of C&Q, there was a live Webinar 5 May 2009 on Implementing the ASTM Standard for Verification (C&Q).

There were also seminars devoted to GAMP and facility renovation, as well as two-day training courses. They are:

- GAMP® Good Practice Guides: Validation of Process Control Systems (VPCS), and Calibration Management, A Risk-Based Approach

- Extreme Facility Makeover: Successful Path to Facility Renovation and Retrofit

- Training – Basic Principles of Computerized Systems Compliance

- Training – Applying the GMPs

For upcoming ISPE Education and Training information, visit www.ISPE.org or call ISPE Members Services at tel: +1-813-960-2105.

ISPE Korea Affiliate in Development

The Korea Affiliate, the newest affiliate to join ISPE's family, is well under way in its development. The Korea Affiliate will be located in South Korea, officially the Republic of Korea and often referred to as Korea.

INTERPHEX Keynote Message: Industry Needs to Reinvent Itself

by Rochelle Runas, ISPE Technical Writer

Expiring patents. An economic slump. New technologies. Regulatory agencies becoming increasingly risk averse. A new administration in Washington.

In a world today that faces these and other uncertainties, one thing's for sure: The pharmaceutical industry needs to reinvent itself, whether it likes it or not.

That was a main message of this year's Keynote at Interphex NY, delivered Tuesday, 17 March at the Jacob Javits Convention Center in New York, New York. The keynote included a presentation by G. Steven Burrill, CEO, Burrill & Co., who shared his vision of the future of healthcare and overriding trends affecting the global industry.

Burrill said the industry will be facing stricter regulatory oversight; the need to prove drug safety and comparative effectiveness (this third standard will begin to emerge); generic biopharmaceuticals, biosimilars; an increase in stem cell funding; and an increase in healthcare IT funding.

So, in 2020, what will the healthcare delivery system look like? Burrill said in the last 2000 years, the pharmaceutical industry has not really changed; people got diseases and they were treated. But, this is not going to be true in the next five to 10 years.

We are changing the nature of the healthcare equation, moving away from a treatment-based system with a one size fits all mentality toward late stage detection and intervention, and a prevention- and wellness-based system. "We've lived in a world of blockbusterology and we're going to live in a world of more targeted, personalized medicines."

Burrill said he envisions a consumer driven healthcare world that includes concepts such as genetic screening, web-based diagnostics, patient-centric self care, and Wal-Mart-like health centers operated by nurse practitioners. Medical tourism will become more popular. For example, it is becoming cheaper to send a patient in need of a hip replacement on a plane to India and put them up in the Four Seasons, than getting the procedure done in local hospital, Burrill said.

What does this kind of world mean to the pharmaceutical industry? According to Burrill, big pharma will disintegrate, a trend already demonstrated by big company mergers. Low margin

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

INTERPHEX Keynote Message

Continued from page 62.

ethical drugs will predominate (China, India, and other low cost manufacturing sites will have an edge). International regulatory agencies will collaborate.

Big pharma today, which is vertically integrated (R&D, manufacturing, distribution, etc.) will disintegrate to be horizontally integrated. The "virtual pharma company" will emerge, with operations located at different sites. Capital will go to where the best opportunities are and partnerships will continue, said Burrill. Also, diseases will have no boundaries, so all companies big and small will be global from day one.

The presentation was followed by a panel discussion with Burrill; Timothy Moore, Senior Vice President, Global Supply Chain, Genentech; Divakar Ramakrishnan, PhD, Executive Director, Manufacturing Science and Technology, Eli Lilly & Co.; and Michael Kowolenko, PhD, Senior Vice President, Biotech Operating Unit, Technical Operations and Product Supply, Wyeth Pharmaceuticals. The panel discussed how they are handling today's challenges.

"We try to balance cost and risk," said Moore. "We put a lot of emphasis on managing risk in our supply chain, balancing the amount of inventory to carry vs. patient need."

Ramakrishnan said his company greatly emphasizes six sigma programs and efficiency.

In the end, biology and technology will be more important than concrete, said Kowolenko.

JPI Features Article on PQLI Legacy Products

The March 2009 issue of the *Journal of Pharmaceutical Innovation*, available online to Members only, features the following articles:

- PQLI®: Current Status and Future Plans
  by John C. Berridge
- PQLI Application of Science- and Risk-based Approaches (ICH Q8, Q9, and Q10) to Existing Products
  by Chris Potter
- Investigation of the Statistical Power of the Content Uniformity Tests Using Simulation Studies
  by Phillip D. Lunney and Carl A. Anderson
- Aqueous Solubility Enhancement Through Engineering of Binary Solid Composites: Pharmaceutical Applications
  by Michael D. Moore and Peter L. D. Wildfong

ISPE Members can access JPI by visiting www.ISPE.org/JPI.

ACTIVE CHEMICAL 65
AES CLEAN TECHNOLOGY 27
BUDZAR INDUSTRIES 39
CAL-CHEM CORP. 37
COMMISSIONING AGENTS 25
CRB CONSULTING ENGINEERS 3
JIM CRUMPLEY & ASSOCIATES 64
ELETTRACQUA 13
EMERSON PROCESS MANAGEMENT 9
ENDRESS + HAUSER 67
FOOD AND DRUG ADMINISTRATION/CDER 65
FARR AIR POLLUTION CONTROL 2
FESTO 45
FIKE CORP. 29
GEA PROCESS ENGINEERING 47
GEA WESTFALIA SEPARATOR 55
GEMU GMBH 63
GLATT GMBH 17
HACH COMPANY 43
HOWORTH AIR TECHNOLOGY 19
HURST CORP. 57
IMA ACTIVE 53
IMA LIFE 35
INTELLIGEN 23
INTERPHEX365 49
MECO 11
NNE PHARMAPLAN 68
OPTIMA MACHINERY 31
PARSONS 5
PHARMACEUTICAL ONLINE 62
PLASCORE 15
QPHARMA 7
TELSTAR 41
WILDEN PUMP & ENGINEERING 51

ENGINEERING PHARMACEUTICAL INNOVATION ISPE

ISPE Brussels Conference Highlights

The ISPE Brussels Conference welcomed more than 180 delegates to update their knowledge and to network at Sheraton Brussels Hotel in Brussels, Belgium on 30 March to 2 April 2009. This year's conference offered a variety of new and enhanced opportunities for attendees to take advantage of. Some of the highlights from the conference were:

- Live webinar presentation from Nick Haycocks in California, USA on the HVAC Good Practice Guide and Good Engineering Practice, as well as the Environmental Cleanliness Classification Quiz that generated lots of discussion at the seminar Heating, Ventilation and Air Conditioning (HVAC): Good Practice and Innovations.

- Regulatory aspects of continuous processing were presented by Dr. Moheb Nasr, Director, Office of New Drug Quality Assessment and Joe Famulare, Deputy Director, Office of Compliance, FDA at the seminar Continuous Processing and Process Intensification for APIs, BPCs and Excipients. Part of the program was developed in conjunction with the International Pharmaceutical Excipients Council (IPEC) since, for the first time, the seminar considered not only APIs/BPCs, but excipients, as well. Delegates were also introduced to the forthcoming ISPE white paper on regulatory issues for continuous processing.

- In a change from the normal format, a one-day interactive Project Management Workshop was held on developing lean, agile project plans. Delegates were working on a detailed project plan over the course of three exercises and received templates as part of the conference documentation allowing them to put them into practice back at the job.

- Andrew Cochrane, UK regulator from MHRA, provided a very useful overview of the current status of the revision of Annex 11 during the seminar GAMP® 5: Part 11, Annex 11 and Industry Hot Topics. The seminar included an interactive workshop on Maintaining Control of Operation, as well as Quality Risk Management in Process Automation, where the links between ICH Q9 and the GAMP® 5 QRM approach were explored. Two new groups were formed during the seminar: a GAMP SIG on outsourcing/offshoring topic, as well as a local GAMP Benelux group with an interactive day of workshops coming up.

- A live webinar presentation was given by Cameron Sipe in the US on the update to the ISPE Water and Steam Baseline® Guide during the Critical Utilities seminar.

The Brussels Conference also hosted a sold-out exhibition with a showcase of the latest new tools and solutions.

The next ISPE events in Europe include Madrid Training from 18 to 21 May; Strasbourg Conference held from 28 September to 1 October; and Dublin Training held from 19 to 22 October 2009.

Our focus: your compliance.

Our innovative technologies combined with our understanding of industry requirements and our commitment to work with you ensure your compliance. You can rely on us to thoroughly assess the risks you face and help you optimize your processes and quality system performance. Endress+Hauser: your partner in creating value. www.endress.com/life_sciences

Endress+Hauser
Instruments International AG
Kägenstrasse 2
4153 Reinach/BL1
Switzerland

Phone +41 61 715 81 00
Fax +41 61 715 25 00
info@ii.endress.com
www.endress.com

Endress+Hauser
People for Process Automation

Classified Advertising

Architects, Engineers – Constructors

CRB Consulting Engineers, 7410 N.W. Tiffany Springs Pkwy., Suite 100, Kansas City, MO 64153. (816) 880-9800. See our ad in this issue.

Parsons, 150 Federal St., Boston, MA 02110. (617)-946-9400. See our ad in this issue.

Cleanroom Products/Services

AES Clean Technology, 422 Stump Rd., Montgomeryville, PA 18936. (215) 393-6810. See our ad in this issue.

Plascore, 615 N. Fairview, Zeeland, MI 49464. (800) 630-9257. See our ad in this issue.

Dust Collectors

Farr APC, 3505 S. Airport Dr., Jonesboro, AR 72401. (866) 530-5474. See our ad in this issue.

Employment Search Firms

Jim Crumpley & Associates, 1200 E. Woodhurst Dr., Bldg. B-400, Springfield, MO 65804. (417) 882-7555. See our ad in this issue.

Robert Drexler Associates, Inc., PO Box 151, Saddle River, NJ 07458. (201) 760-2300. See our ad in this issue.

Instrumentation

Hach Ultra Analytics, 5600 Lindbergh Dr., Loveland, CO 80539. (970) 663-1377. See our ad in this issue.

Passivation and Contract Cleaning Services

Active Chemical Corp., 4520 Old Lincoln Hwy., Oakford, PA 19053. (215) 676-1111. See our ad in this issue.

Cal-Chem Corp., 2102 Merced Ave., South El Monte, CA 91733. (800) 444-6786. See our ad in this issue.

Processing Systems

GEA Niro Pharma Systems, 9165 Rumsey Rd., Columbia, MD 21045. See our ad in this issue.

Optima Machinery Corp., 1330 Contract Dr., Green Bay, WI 54304. See our ad in this issue.

Pumps

Wilden Pump & Engineering, 22069 Van Buren St., Grand Terrace, CA 92313. (909) 422-1730. See our ad in this issue.

Rupture Discs

Fike Corp., 704 SW 10th St., Blue Springs, MO 64015. (816) 655-4546. See our ad in this issue.

Sterile Products Manufacturing

Process Tek - *Sterility by Design*
INNOVATION, RELIABILITY & PROFESSIONALISM
R&D, Validation, GMP Auditing,
HACCP, Problem Solving and Training
for sterile products, packages & processes
Kailash S. Purohit, PhD
www.processtek.net • kaipurohit@processtek.net

Temperature Control Systems

Budzar Industries, 38241 Willoughby Pkwy., Willoughby, OH 44094, (440) 918-0505. See our ad in this issue.

Validation Services

Commissioning Agents, Inc., 1515 N. Girls School Rd., Indianapolis, IN 46214. (317) 710-1530. See our ad in this issue.

Valves

Gemu GmbH & Co., Fritz-Mueller-Str. 6-8, D-74653 Ingelfingen, Germany. +49 7940123-0. See our ad in this issue.

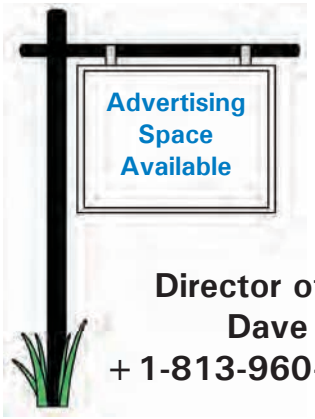
Vial Traying Systems

Hurst Corp., Box 737, Devon, PA 19333. (610) 687-2404. See our ad in this issue.

Water Treatment

Elettracqua Srl, Via Adamoli 513, 16141 Genova, Italy. +39 0108300014. See our ad in this issue.

MECO, 12505 Reed Rd., Suite 100, Sugar Land, TX 77478. (800) 421-1798. See our ad in this issue.



Call ISPE
Director of Sales
Dave Hall at
+1-813-960-2105.

Inc. 1955

ACTIVE CHEMICAL CORP.

SPECIALISTS IN . . .

— LABORATORY CONTROLLED —

- CHEMICAL CLEANING SERVICES OF HEAT EXCHANGE EQUIPMENT
- PASSIVATION OF STAINLESS STEEL PIPING
- STERILIZATION OF PIPING & EQUIPMENT
- SOFTENERS & DEIONIZERS
- RECONDITIONING OF FILTERS & ION EXCHANGERS
- WATER TREATING CONSULTANTS
- BOILER & COOLING WATER CHEMICALS

SERVICE CONTRACTS

(215) 676-1111

4520 Old Lincoln Hwy., Oakford, PA 19053

FDA

Division Director Position

U.S. Department of Health and Human Services / Food and Drug Administration

SUBMIT RESUME TO:

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of New Drug Quality Assessment (ONDQA)
ATTENTION: Erik Henrikson
10903 New Hampshire Ave., Bldg. 21 Rm. 2669
Silver Spring, MD 20993-0002

For additional questions please call 301-796-4110

The Food and Drug Administration is recruiting a Division Director for the Office of New Drug Quality Assessment (ONDQA), Office of Pharmaceutical Science, Center for Drug Evaluation and Research. The mission of ONDQA is to assess the critical quality attributes and manufacturing processes of new drugs, establish quality standards to assure safety and efficacy, and facilitate new drug development. Strong organizational and executive leadership skills are very desirable. The Division Director is responsible for providing scientific direction and for planning, managing, and organizing pharmaceutical quality assessment of drug products assigned to the division to ensure safety, purity, potency and effectiveness.

DESIRED QUALIFICATION: A Ph.D. degree in chemistry and/or other related disciplines (e.g., biochemistry, pharmaceutics, industrial pharmacy, engineering), with appropriate experience in pharmaceutical development, manufacturing, and regulations, is desired. Candidates for Civil Service must be U.S. citizens. Graduates of foreign colleges/universities must provide proof of U.S. education equivalency.

SALARY RANGE: Civil Service GS-15 at $120,830 to $153,200 per annum with an excellent benefits package and training opportunities. For an exceptionally qualified and experienced candidate, additional compensation may be provided

THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION IS AN EQUAL OPPORTUNITY EMPLOYER AND HAS A SMOKE FREE ENVIRONMENT

ACTIVE CHEMICAL 65
AES CLEAN TECHNOLOGY 27
BUDZAR INDUSTRIES 39
CAL-CHEM CORP. 37
COMMISSIONING AGENTS 25
CRB CONSULTING ENGINEERS 3
JIM CRUMPLEY & ASSOCIATES 64
ELETTRACQUA 13
EMERSON PROCESS MANAGEMENT 9
ENDRESS + HAUSER 67
FOOD AND DRUG ADMINISTRATION/CDER 65
FARR AIR POLLUTION CONTROL 2
FESTO 45
FIKE CORP. 29
GEA PROCESS ENGINEERING 47
GEA WESTFALIA SEPARATOR 55
GEMU GMBH 63
GLATT GMBH 17
HACH COMPANY 43
HOWORTH AIR TECHNOLOGY 19
HURST CORP. 57
IMA ACTIVE 53
IMA LIFE 35
INTELLIGEN 23
INTERPHEX365 49
MECO 11
NNE PHARMAPLAN 68
OPTIMA MACHINERY 31
PARSONS 5
PHARMACEUTICAL ONLINE 62
PLASCORE 15
QPHARMA 7
TELSTAR 41
WILDEN PUMP & ENGINEERING 51

ENGINEERING PHARMACEUTICAL INNOVATION ISPE

ISPE Brussels Conference Highlights

The ISPE Brussels Conference welcomed more than 180 delegates to update their knowledge and to network at Sheraton Brussels Hotel in Brussels, Belgium on 30 March to 2 April 2009. This year's conference offered a variety of new and enhanced opportunities for attendees to take advantage of. Some of the highlights from the conference were:

- Live webinar presentation from Nick Haycocks in California, USA on the HVAC Good Practice Guide and Good Engineering Practice, as well as the Environmental Cleanliness Classification Quiz that generated lots of discussion at the seminar Heating, Ventilation and Air Conditioning (HVAC): Good Practice and Innovations.

- Regulatory aspects of continuous processing were presented by Dr. Moheb Nasr, Director, Office of New Drug Quality Assessment and Joe Famulare, Deputy Director, Office of Compliance, FDA at the seminar Continuous Processing and Process Intensification for APIs, BPCs and Excipients. Part of the program was developed in conjunction with the International Pharmaceutical Excipients Council (IPEC) since, for the first time, the seminar considered not only APIs/BPCs, but excipients, as well. Delegates were also introduced to the forthcoming ISPE white paper on regulatory issues for continuous processing.

- In a change from the normal format, a one-day interactive Project Management Workshop was held on developing lean, agile project plans. Delegates were working on a detailed project plan over the course of three exercises and received templates as part of the conference documentation allowing them to put them into practice back at the job.

- Andrew Cochrane, UK regulator from MHRA, provided a very useful overview of the current status of the revision of Annex 11 during the seminar GAMP® 5: Part 11, Annex 11 and Industry Hot Topics. The seminar included an interactive workshop on Maintaining Control of Operation, as well as Quality Risk Management in Process Automation, where the links between ICH Q9 and the GAMP® 5 QRM approach were explored. Two new groups were formed during the seminar: a GAMP SIG on outsourcing/offshoring topic, as well as a local GAMP Benelux group with an interactive day of workshops coming up.

- A live webinar presentation was given by Cameron Sipe in the US on the update to the ISPE Water and Steam Baseline® Guide during the Critical Utilities seminar.

The Brussels Conference also hosted a sold-out exhibition with a showcase of the latest new tools and solutions.

The next ISPE events in Europe include Madrid Training from 18 to 21 May; Strasbourg Conference held from 28 September to 1 October; and Dublin Training held from 19 to 22 October 2009.

On-Line Exclusive Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2009, Vol. 29 No. 3

This article presents the responsibilities, structure, and affiliated organizations for the China State Food and Drug Administration (SFDA).

China State Food and Drug Administration (SFDA) – Responsibilities, Internal Structure, and Affiliated Organizations

by Jason Tang

Introduction

Regulatory responsibilities in Greater China are split between a number of organizations on the mainland and other regions. These include the State Food and Drug Administration (SFDA), the Ministry of Agriculture, the pharmaceutical service of the Department of Health of the Hong Kong Special Administrative Region, and the Macau Health Authority with the Departamento dos Assuntos Farmacêuticos or Pharmaceutical Affairs Department. Taiwan Regulatory Affairs are controlled by the Taiwan Department of Health.

This article provides an overview of the responsibilities and structure of the SFDA.

Main Responsibilities

The responsibility for regulating drugs has undergone significant changes in the past decade in China.

Originally part of the domain of the Ministry of Health until 1998, the State Drug Administration (SDA) was formed as a separate bureau in 1999. This Agency's name was changed in 2003 to the State Food and Drug Administration (SFDA) and remained separate. In July 2007, irregularities within the organization called China's drug manufacturing practices into question. In March 2008, the SFDA was amalgamated back into the Ministry of Health.

The SFDA develops policies and plans for the supervision of drugs, medical devices, cosmetics, and food safety in the consumer contact sector and supervises their implementation. It participates in drafting relevant laws, regulations, and normative documents.

The Agency develops good practices for drugs and medical devices in the areas of research, manufacturing, distribution, and use and supervises their implementation. The Agency also develops good practices for food safety in the consumer contact sector and supervises its implementation.

The Agency monitors food safety in the consumer contact sector and conducts investigations. The Agency releases information related to the supervision of food safety in the consumer contact sector. The Agency is in charge of hygiene licensing and safety supervision of food in the consumer contact sector, as well as cosmetic hygiene licensing, hygiene supervision, and relevant review and approval work of cosmetics.

The SFDA is in charge of the administrative and technical supervision and registration of drugs and medical devices. It develops relevant national standards and supervises their implementation.

The Agency conducts ADR monitoring and adverse event monitoring of medical devices; is responsible for drug and medical device re-evaluation and withdrawal; engages in developing the national essential medicine list, assisting relevant authorities to adopt the national essential medicine system; and organizes the implementation of the classification system for prescription drugs and OTC drugs.

The Agency is in charge of developing regulations for Traditional Chinese Medicines (TCMs) and ethno-medicines, supervising their implementation. The Agency develops quality standards of TCMs and ethno-medicines, Good Agricultural Practices for Chinese crude drugs

and Preparation Standards for Chinese crude drugs, supervising their implementation, and enforces the protection system for certain traditional Chinese medicines.

The SFDA supervises the quality and safety of drugs and medical devices, regulating radioactive pharmaceuticals, narcotics, toxics, and psychotropics. The Agency releases quality and safety information for drugs and medical devices, and is responsible for investigating and punishing illegal activities in food safety in the consumer contact sector and in use of drugs, medical devices, and cosmetics in the areas of research, manufacturing, and distribution.

The Agency directs local food and drug authorities on supervision, administration, emergency response, inspection, and information construction.

Developing and improving the qualification system for licensed pharmacists is the responsibility of the Agency in addition to supervising and directing the registration of licensed pharmacists.

The SFDA conducts international exchanges and cooperation related to food and drug regulation, in addition to overseeing other work assigned by the State Council and the Ministry of Health.

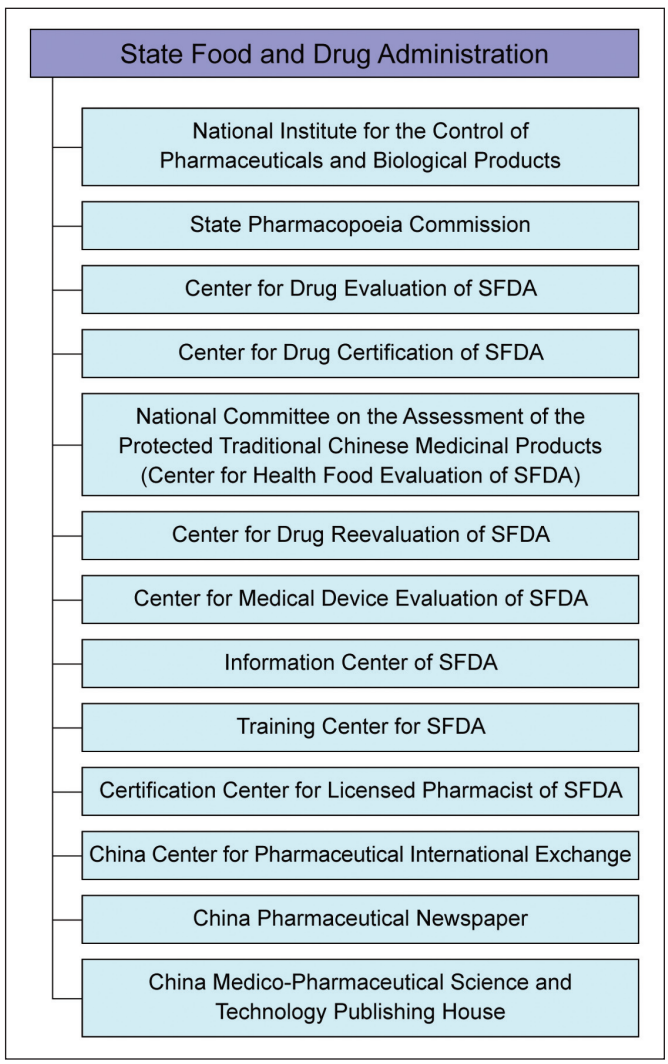


Figure 1. Affiliated organizations.

The Internal Structure of SFDA

General Office (Department of Financial Planning)

The department of Financial Planning is responsible for the daily government affairs operations, including documents and telegrams, meetings affairs, confidential affairs, and archive management. The Department manages security and secrecy work, openness of government affairs, dealing with complaint letters and visits, statistics management, etc. The department develops and implements the planning and finance management system of headquarters and affiliated organizations. It is also responsible for managing administrative charges and instructing information construction in the regulatory system.

There are eight divisions under this Department:

1. Division of General Affairs (Office of Complaint Letters and Visits)
2. Division of Secretaries I
3. Division of Secretaries II
4. Division of Emergency Management
5. Division of Archives
6. Division of Development and Planning
7. Division of Budget Management
8. Division of Government Financial Affairs

Department of Policy and Regulations

The Department of Policy and Regulations engages in the development of laws, regulations, and provisions related to the Food and Drug Administration. It supervises the administrative law-enforcement and oversees administrative reconsideration, pleading, and hearing, etc. The Department also provides news briefings.

There are four divisions under this Department:

1. Division of General Affairs (Office of Administrative Reconsideration)
2. Division of Regulations
3. Division of Policy Research
4. Division of News (Office of News)

Department of Food License

The Department of Food License is responsible for managing hygiene licenses for food and cosmetics; developing relevant rules for the implementation of hygiene license for food and cosmetics; developing hygiene standards and technical guidelines for cosmetics; examining and approving the law regarding the use of new raw materials for cosmetics, manufacture of domestic cosmetics for special use, and the first time import of cosmetics, etc.

There are three divisions under this Department:

1. Division of Food
2. Division of Health Food
3. Division of Cosmetics

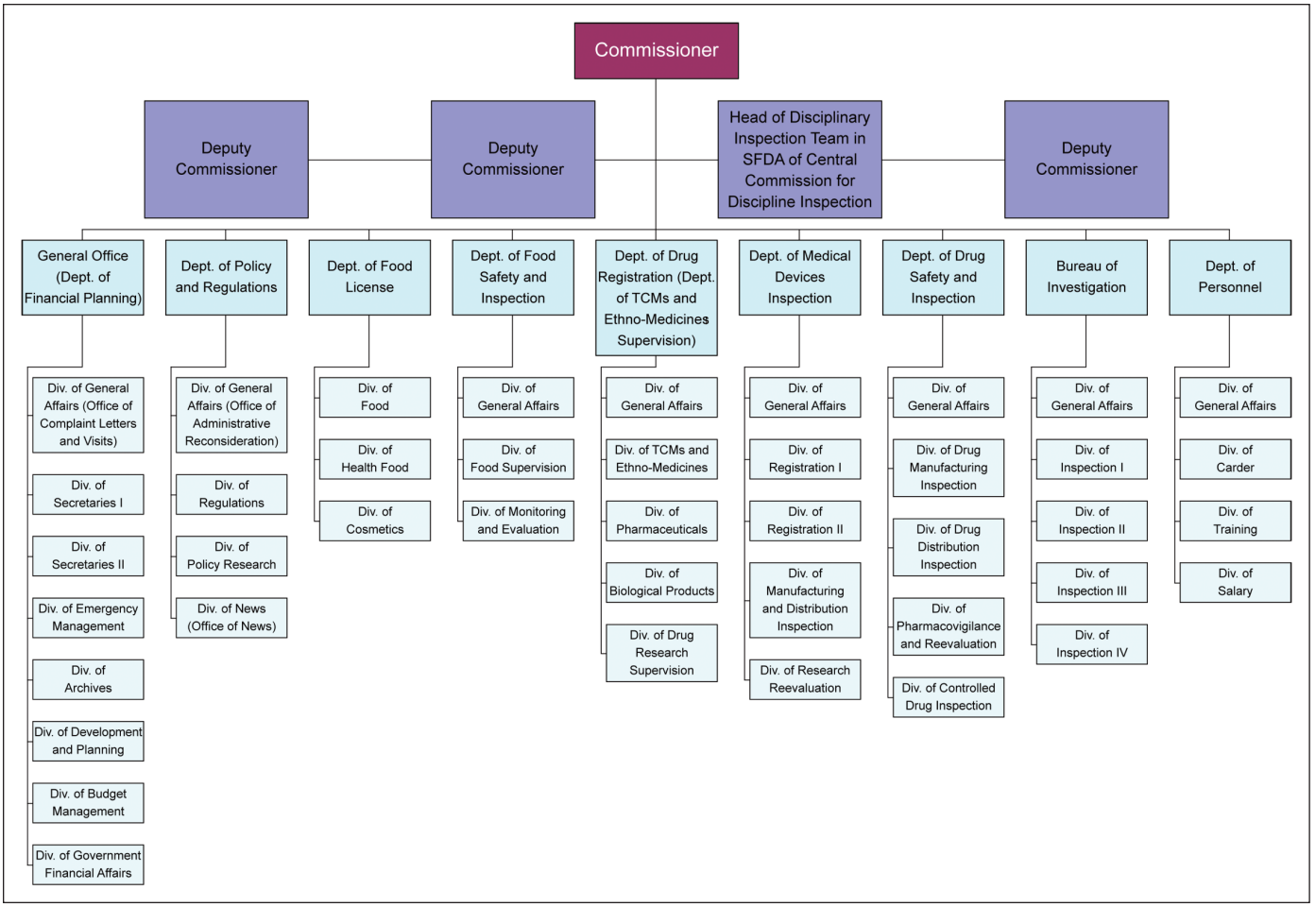


Figure 2. SFDA structure.

Department of Food Safety and Inspection

The Department of Food Safety and Inspection oversees the safety supervision of food in the consumer contact sector; develops good practices for food safety in the consumer contact sector and supervises its implementation; monitors food safety in the consumer contact sector and conducts investigations; releases information related to the supervision of food safety in the consumer contact sector; evaluates and examines the safety of cosmetics by law; and supervises the hygiene of cosmetics.

There are three divisions under this Department:

1. Division of General Affairs
2. Division of Food Supervision
3. Division of Monitoring and Evaluation

Department of Drug Registration (Department of TCMs and Ethno-Medicines Supervision)

The Department of Drug Registration organizes the development of national drug standards, product list of immediate packaging materials and containers to drugs, the requirements and standards for their medical use, and is responsible for their registration; develops preparation standards for the prepared slices of Chinese crude drugs and supervise their implementation; develops the list of OTC drugs; organizes the development of good practices for non-clinical and clinical drug trials, supervising their implementation; and implements the protection system for traditional Chinese medicines.

There are five divisions under this Department:

1. Division of General Affairs
2. Division of TCMs and Ethno-Medicines
3. Division of Pharmaceuticals
4. Division of Biological Products
5. Division of Drug Research Supervision

Department of Medical Devices Inspection

The Department of Medical Devices Inspection organizes the development of national medical device standards and supervises their implementation; develops the list of classified medical devices; is in charge of registration and regulation of medical devices; develops good practices for clinical trials, manufacturing, and distribution of medical devices, supervising their implementation; supervises the licensing of medical devices manufacturing and distribution; and organizes the adverse events monitoring, reevaluation, and elimination of medical devices.

There are five divisions under this Department:

1. Division of General Affairs
2. Division of Registration I
3. Division of Registration II
4. Division of Manufacturing and Distribution Inspection
5. Division of Research and Reevaluation

Department of Drug Safety and Inspection

The Department of Drug Safety and Inspection develops good practices for Chinese crude drug production, drug manufacturing and distribution, and preparations produced by medical institutions, supervising their implementation; engages in developing the national essential medicines list; organizes the implementation of the drug classification system; controls radio-active drugs, narcotics, toxics and psychotropics, and precursor chemicals; supervises the licensing of drug manufacturing, drug distribution, and pharmaceutical preparations in medical institutions; and organizes the adverse reaction monitoring, reevaluation, and elimination of drugs.

There are five divisions under this Department:

1. Division of General Affairs
2. Division of Drug Manufacturing Inspection
3. Division of Drug Distribution Inspection
4. Division of Pharmacovigilance and Reevaluation
5. Division of Controlled Drugs Inspection

Bureau of Investigation

The Bureau of Investigation develops and implements the investigation system for the regulation of food safety in the sections of consumption, drugs, medical devices, and cosmetics; oversees the market inspection of Chinese crude drugs; guides and supervises relevant local departments in investigation and enforcement, emergency management, advertisement examination and approval, product recall, case investigating, and prosecuting; and organizes the investigation and prosecution of illegal activities.

There are five divisions under this Department:

1. Division of General Affairs
2. Division of Inspection I
3. Division of Inspection II
4. Division of Inspection III
5. Division of Inspection IV

Department of Personnel

The Department of Personnel is in charge of personnel affairs for headquarters staff and affiliated institutions; develops and improves the qualification system for licensed pharmacists; and supervises and guides registration of licensed pharmacists.

There are four divisions under this Department:

1. Division of General Affairs
2. Division of Carder
3. Division of Training
4. Division of Salary

Department of International Cooperation (Office for Hong Kong, Macao, and Taiwan Affairs)

The Department of International Cooperation organizes and conducts international exchanges and cooperation in food and drug regulation; and is responsible for managing exchanges and cooperation with Hong Kong, Macao, and Taiwan affairs in food and drug regulation.

There are three divisions under this Department:

1. Division of International Organization
2. Division of European, Asian, and African Affairs
3. Division of American and Oceanian Affairs

Summary

The SFDA was formed on the basis of the State Drug Administration and is directly under the State Council of the People's Republic of China, which is responsible for the comprehensive supervision of the safety management of food, health food, and cosmetics. The SFDA is the competent authority of drug regulation in mainland China; however, it is not responsible for regulating pharmaceutical ingredients manufactured and exported by chemical companies.

On-Line Exclusive Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
May/June 2009, Vol. 29 No. 3

Europe

Czech Republic

GMP for Manufacture of Medicinal Substances[1]

The SIDC has issued Provision VYR-26 Version 1: Instructions for Good Manufacturing Practice in the Manufacture of Medicinal Substances, 12 March 2009 to determine the requirements for good manufacturing practices in the Czech Republic.

Denmark

Danish Agency Updates "Qualified Person" Guidelines[2]

The Danish Medicines Agency has published updated guidelines explaining its requirements and expectations concerning the pharmaceutical company "qualified person."[1] Although classified as guidelines, the list is based on the requirements of the main European Union directives on medicines for human and veterinary use (Directives 2001/83/EC and 2001/82/EC respectively).

Under the aforementioned Directives manufacturing authorization holders in the EU are required to have at least one qualified person always at their disposal. The role of the qualified person is critical; his or her main responsibility in pharmaceutical production is to certify that each batch of finished product that is released for sale or supply in the EU/European Economic Area has been produced and tested in accordance with the relevant EU directives, good manufacturing practices, and the provision of the marketing authorization.

The qualified person must have experience in the areas of production, quality assurance, or quality control. The relationship between the qualified person and the company must be "of significance" and requires a notice of permanent or contractual employment. This means that the individual must spend a minimum of 10 hours per week in the company. However, if the firm in question is small or only produces in limited operations, this time limit may be amended. The qualified person must have sufficient knowledge of the quality system in place in the company and must furthermore be a resident of the EEA.

Danish Medicines Agency Monitors Compliance with API Rules[3]

The Danish Medicines Agency has launched a project to monitor how companies comply with rules governing manufacture and handling of active pharmaceutical ingredients.[1] The main purpose of the project is to improve the possibilities for achieving efficient control of APIs via co-operation between pharmaceutical companies and the agency.

In Denmark, as in other European Union countries, APIs used in marketed medicines must be manufactured in accordance with EU good manufacturing practice. The DMA will conduct spot checks to ensure compliance with the rules. In 2009, it plans to inspect 15 API manufacturers and carry out laboratory analyses of APIs from 50 manufacturers selected by its Medicines Control Division. Before inspecting the API manufacturers, the agency will inspect Danish manufacturers of finished products that use products from one of the 15 API manufacturers. It says that it will be possible during these short inspections to discuss challenges and possible special risk areas relating to API manufacturers. Relevant audit reports also will be discussed.

Germany

German Industry Criticizes Proposed Revisions to Pharmaceutical Act – Update[4]

The German pharmaceutical industry has criticized some of the government's proposed amendments to the Pharmaceutical Act, which would oblige them to supply wholesalers.[1,2] The aim of the health ministry is to guarantee the provision of medicines to the public as quickly as possible via wholesalers and pharmaceutical manufacturers.

In its draft amendment proposals published in December 2008,[3] the ministry noted that within the distribution chain, only pharmacies were subject to a contractual obligation to supply the public. However, in order to guarantee the provision of medicines, pharmacies had to themselves be adequately supplied by wholesalers and manufacturers, it reasoned. Hence, the ministry is now seeking to extend the contractual obligation to these two parties. The pharmaceutical industry views the revision and compulsory supply of wholesalers as an encroachment on its commercial freedom.

It has been noted that these changes would lead to less red tape and greater harmonisation, both of which would facilitate work for internationally acting companies. For example, applicants would be able to file their entire dossier in English, apart from product information, such as the label, summary of product characteristics, and package leaflet.

United Kingdom

GMP[1]

The MHRA have released guidelines part of the MHRA Good Manufacturing Practice Risk-Based Inspection Process. The new guidelines are intended for sites holding or named on a United Kingdom manufacturing license in order to help them to complete the compliance report form.

The compliance report must be completed in advance of an inspection and aims at informing the inspector of the changes on site. This compliance report is part of the MHRA Good Manufacturing Practice Risk-Based Inspection Process and will be coming into force on 1 April 2009.

International

China

Advice on Quality Testing of Re-Packing of Import Drug[1]

A notification has been issued that requests that product imported into China and repacked should be up to the quality specifications for import product approved by SFDA. The foreign manufacturer must take responsibility for product repacked on import.

Egypt

Strict Rules for Wholesalers and Warehouses[5]

The Egyptian minister of health has issued a decree that aims to combat counterfeit drugs, control price manipulations, and tighten up the licensing rules for pharmaceutical wholesale distribution companies and phar-

maceutical warehouses.[1] The decree, which entered into force on 19 January, updates the existing pharmaceutical law (127/1955) and replaces decree 151/2006 on wholesaler/warehouse licensing.

Under the decree, wholesale medicines are only allowed to be handled by licensed pharmaceutical wholesale distribution companies or pharmaceutical warehouses (companies/warehouses). In addition, such companies/warehouses are now subject to inspections by the Central Administration of Pharmaceutical Affairs (CAPA) before being granted a license.

The decree explicitly states how a warehouse should be set up, for example, it must have an area of at least 500 square meters, as well as a separate entrance and appropriate storage facilities (warehouses licensed prior to 19 January will have until 30 June 2010 to comply with the area requirement). They also must have computerized electronic data storage systems that keep records of inventory, purchases, and sales. Companies/warehouses must obtain only registered medicines from licensed pharmaceutical manufacturing companies or licensed importing offices with which they have distribution contracts. CAPA inspectors have the right to see these contracts and it is forbidden to handle or store any products not covered by these contracts.

Taiwan

Taiwan's Plan to Create New Regulatory Body[6]

Two Taiwanese legislative committees have jointly approved a draft bill put forth by the country's executive branch (the Executive Yuan) to establish a new Food and Drug Administration office that would bring a number of key regulatory and product safety activities under one roof.[1,2] For the Taiwan FDA (TFDA) to become functional, the bill now has to be cleared by the Legislative Yuan.

The TFDA Organic Law envisages merging four departments that are presently under the control of the Department of Health into one single entity to form the TFDA: the Bureau of Food Safety; the Bureau of Pharmaceutical Affairs; the Bureau of Food and Drug Analysis; and the National Bureau of Controlled Drugs. The process to establish the TFDA gathered momentum in September 2008 after melamine-contaminated milk powder made its way into Taiwan from China.

United States

US FDA opens offices in India, Latin America, and Europe[7]

As part of its efforts to better guarantee the quality of food, drug, and medical device imports, the US Food and Drug Administration has opened offices in India, Latin America (Costa Rica), and Europe (Belgium).[1,2] The agency had already opened offices in China and there are plans to set up offices elsewhere in Latin America and also in the Middle East.[3] Deployment of FDA personnel at these overseas offices will allow the agency to carry out frequent inspections of manufacturing units exporting products to the US market.

India is the fourth-largest exporter by volume of drugs and biologics, especially generic pharmaceuticals to the US. The FDA's Indian office will provide technical advice, conduct inspections of facilities that export to the US, and "work with Indian government agencies and the private sector to develop certification programs to allow the efficient flow of safe... FDA-regulated goods between the US and India."

Latin American countries are key trade partners for the US and the FDA's presence in the region will begin capacity-building in the regulation of drugs, medical devices, and food. The agency also plans to set up offices in Mexico and South America later in the year.

The FDA's European office, in Brussels, will spearhead regulatory collaboration with the European Commission. Its remit will be to build on the existing robust relationships with the European Medicines Agency, the European Food Safety Authority, the European Commission, and the individual member state authorities.

Import Safety[8]

The Food and Drug Administration and several other US government agencies have drafted a guide on good importer practices to help ensure that health products finding their way into the US meet required standards.[1-3] The guidance is designed to help importers detect and prevent potential problems at critical points along the life cycle of a product.

The FDA notes that hazards can be introduced at any point in a product's lifecycle – such as designing, manufacturing, processing, packing, receiving, storing, transporting, importing, and distributing – that may put consumers at risk. The guidance is designed to help importers anticipate potential sources of product hazards and offer preventive controls.

In general, the guidance recommends that importers should know the producer of the foreign products they purchase and any other manufacturers with which they do business, such as consolidators, trading companies, and distributors; understand the products that they import and the vulnerabilities associated with these products; understand the hazards that may arise during the product life cycle; and ensure proper control and monitoring of these hazards.

United States Pharmacopeial (USP) Looks to Closer Collaboration with FDA[9]

The USP joins other consumer and healthcare organizations that have urged President Obama's administration to work with Congress to increase funding for the FDA. "Failure to give the FDA these resources jeopardizes the Obama Administration's ability to achieve its broad healthcare quality goals," warns the USP.

In strengthening the science base of the FDA's decision-making, agency managers must have greater access to scientific expertise, recommends the USP. This could include making better use of the National Academy of Sciences and the USP, which already collaborate with the agency in the development of standards. A stronger focus on the risk assessment of new drugs is also suggested.

Standards are regarded as critical to the FDA's regulatory role. Greater emphasis on the role of public standards

and associated technical aids in drug and food quality would enhance quality assurance, the USP believes. Closer collaboration between the FDA and standard-setting organizations could help fill gaps in existing standards and increase recognition of standards, potentially bringing national uniformity to all drugs and food ingredients, while conserving FDA resources. Collaborative efforts also could include third-party verification and the USP's nascent verification programs might prove a useful model for ensuring the safety of imports.

On the subject of follow-on biologicals (known also as biogenerics or biosimilars), the USP believes that it has the authority to develop or revise monographs for these products if a regulatory pathway is established through amendments to the Public Health Service Act.

Finally, the USP believes that the FDA should enhance its activities in the international community to promote the competitiveness and standing of the US in the world. Among initiatives put forward are that the commissioner should assess the effectiveness of the International Conference on Harmonisation and enhance work with other countries' drug control laboratories.

Separately, the USP Convention has announced new standards for heparin and glycerin, both of which have been involved in recent episodes of adulterated products resulting in patient deaths.

Revisions to the monographs for heparin sodium and heparin sodium injection are available for public review and comment until 15 May 2009 and are due to become official in August 2009.[3,4]

A revised standard for glycerin that provides a new test for manufacturers to use in preventing glycerin diluted with diethylene glycol (DEG) from entering the US drug supply also has been issued for public comment and became official on 1 May 2009.[6]

FDA Explains Strict Rules for Approving Drugs from GE Animals[10]

Final guidance on the regulation of Genetically Engineered (GE) animals issued by the US Food and Drug Administration's Center for Veterinary Medicine recommends a rigorous and transparent review process for medicines and other therapeutic goods derived from such animals (also called biopharm or transgenic animals) before they are approved.[1] GE animals can produce pharmaceutical proteins and replacement tissues in their milk, eggs, and blood, which can be used in the treatment of human disease. They also can be used for developing animal models for human diseases.

Among other things, the CVM, which is responsible for the oversight of GE animals, sets out the requirements for investigational use of GE animals and for submitting new animal drug applications (NADAs); explains the process for completing preapproval assessments for GE animals; outlines postapproval responsibilities (e.g., recordkeeping, submission of annual reports); and addresses environmental considerations. The CVM encourages developers of such animals to contact the centre early in the development process.

The guidance is based on the Federal Food, Drug, and Cosmetic Act's framework for new animal drugs and only pertains to GE animals containing heritable recombinant DNA constructs (i.e., intended to affect the structure or function of the body of the GE animal, regardless of the intended use of products that may be produced by those animals). The CVM says that although many of the recommendations in the document may be relevant to animals bearing non-heritable rDNA constructs (e.g., intended for use in gene therapy), it may issue separate guidance on the regulation of those animals.

On a separate note, the FDA has granted its first-ever approval of a biological drug produced by a GE animal; the product is derived from the milk of a GE animal for treating people with hereditary antithrombin deficiency, a rare clotting disorder associated with severe complications.[3,4] The drug, GTC Biotherapeutics' ATryn, has been given an orphan designation because hereditary antithrombin deficiency occurs in a small population. As part of its review of the GE goats used to produce the drug, the CVM assessed the safety of the rDNA construct to the animal, including a full review of the construct and its stability in the genome of the goats over seven generations. The CVM also reviewed and concurred with the sponsor's plan to continue to monitor the construct and its expression for the lifetime of the approved product.

The drug is already approved for use in Europe[1] and was accorded a priority review by the FDA in September 2008.

South Africa

GMP

The Medicine Control Council from South Africa released the new version 4 of the Guide to Good Manufacturing Practice for Medicines amending Radiopharmaceuticals (Annex 3) and Herbal Medicinal Products (Annex 7). The standards in this guide apply to medicines and similar products intended for human and veterinary use and are to maintain high standards of quality assurance in the development and to facilitate manufacture and control of medicinal products.

References

1. www.idrac.com
2. **RAJ issue: Vol 20 No 0409:** Guidelines from the Danish Medicines Agency on its expectations of a qualified person in a pharmaceutical company, 17 February 2009, www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=14732.
3. **RAJ issue: Vol 20 No 0409:** DMA press release, 12 March 2009, www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=14850.
4. **RAJ issue: Vol 20 No 0309:**
   1. VFA press release, 19 January 2009, www.vfa.de/de/inline/nachrichten/pm-005-2009-warum-keine-wettbwerbliche-loesung.html.
   2. BPI press release, 19 January 2009, www.bpi.de/Default.aspx?tabindex=1&tabid=491&p=1&tp_id=335&name=pmNews&control=ipopup.
   3. Proposed amendments to Phar-

maceutical Act, 22 December 2008, www.bmg.bund.de/cln_117/nn_1168248/SharedDocs/Downloads/DE/GV/GT/Entwuerfe/publizierte-Entwuerfe/Referentenentwurf__15.AMG__Novelle,templateId=raw,property=publicationFile.pdf/Referentenentwurf_15.pdf.

5. **RAJ issue: Vol 20 No 0309:**
   1. MoHP Decree No 25, 18 January 2009.
   2. MoHP workshop on Intellectual Property Enforcement and Combating Trade in Counterfeit Medicines and Medical Devices, 12-19 January 2009.
6. **RAJ issue: Vol 20 No 2 February 2009:**
   1. Taiwan Central News Agency, First review of draft FDA Act approved by legislative Committees, 18 December 2008, www.cnanews.gov.tw/cnaeng.
   2. *Scrip World Pharmaceutical News* online, 21 June 2007.
7. **RAJ issue: Vol 20 No 2 February 2009:**
   1. HHS press release, 15 January 2009, www.hhs.gov/news/press/2009pres/01/20090115a.html.
   2. HHS press release, 7 January 2009, www.hhs.gov/news/press/2009pres/01/20090107a.html.
   3. *The Regulatory Affairs Journal – Pharma*, 2008, **19**(11), 797-798.
8. **RAJ issue: Vol 20 No 2 February 2009:**
   1. *Federal Register*, 13 January 2009, **74**(8), 1692-1693, http://edocket.access.gpo.gov/2009/pdf/E9-453.pdf.
   2. FDA press release, 12 January 2009, www.fda.gov/bbs/topics/NEWS/2009/NEW01941.html.
   3. FDA, Good Importer Practices Draft Guidance, 12 January 2009, www.fda.gov/oc/guidance/goodimportpractice.html.
9. **RAJ issue: Vol 20 No 0309:**
   3. *Pharmacopeial Forum*, Mar-Apr 2009, Vol. **35**(2), 1-10, www.usp.org/pdf/EN/hottopics/heparinSodiumMonograph.pdf.
   4. *Pharmacopeial Forum*, Mar-Apr 2009, Vol. **35**(2), 1-3, www.usp.org/pdf/EN/hottopics/heparinSodiumInjectionMonograph.pdf
   6. USP, Revision Bulletin, 4 February 2009, www.usp.org/USPNF/notices/glycerinMonographAnnouncement.html.
10. **RAJ issue: Vol 20 No 0309:**
    1. FDA, Guidance for Industry: Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs [#187], 15 January 2009, www.fda.gov/cvm/Guidance/fguide187.pdf.
    3. FDA press release 6 February 2009, www.fda.gov/bbs/topics/NEWS/2009/NEW01952.html.
    4. GTC Biotherapeutics press release, 9 January 2009, www.gtcbio.com/pressreleases/pr010909.html.
    5. *The Regulatory Affairs Journal – Pharma*, 2006, **17**(7), 456-457.

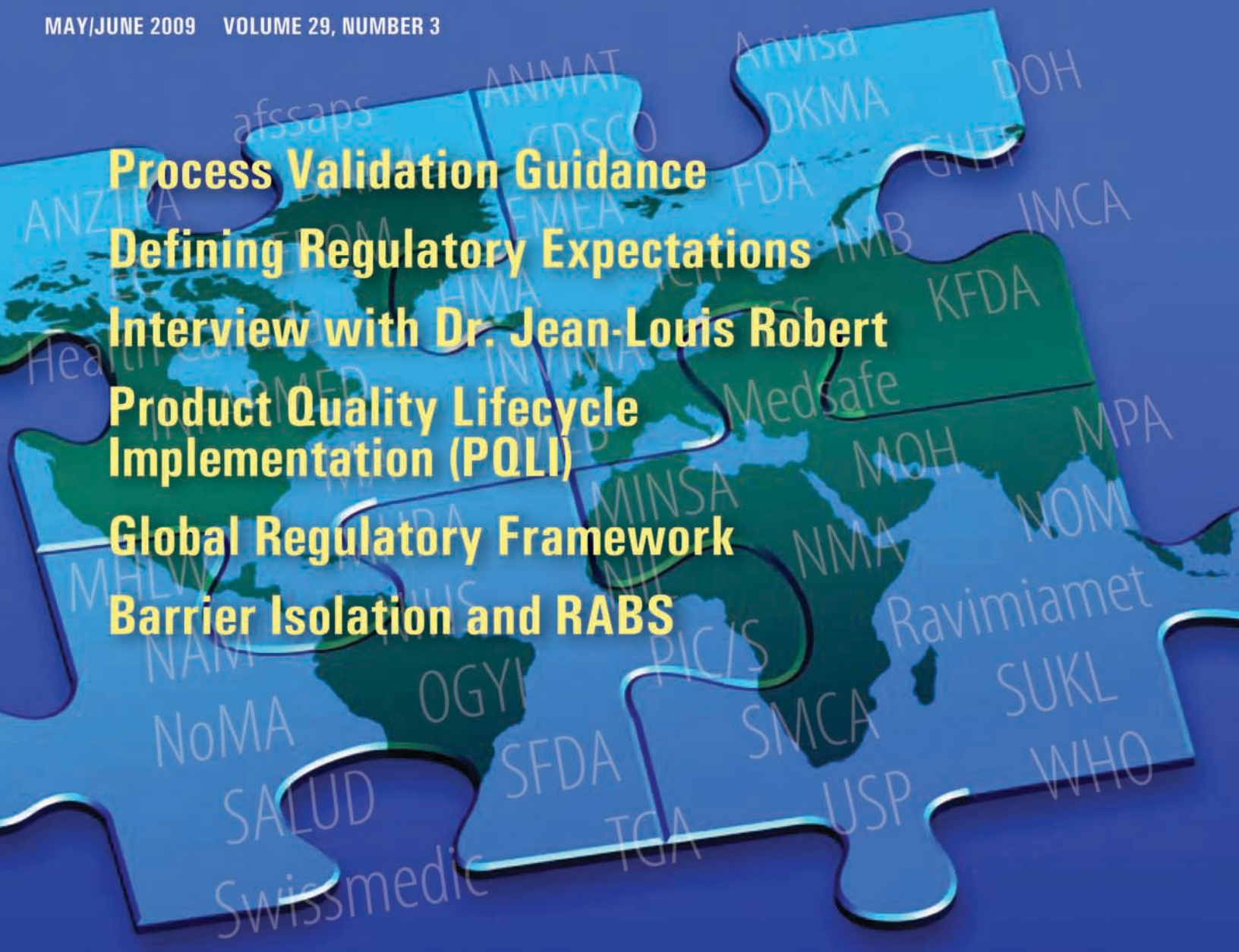
This information was provided by Frank Sayala and Rohini Chari, Pharmaceutical Research Associates (UK).

The Global Information Source for Pharmaceutical Science and Manufacturing Professionals

PHARMACEUTICAL ENGINEERING®

THE OFFICIAL MAGAZINE OF ISPE

MAY/JUNE 2009 VOLUME 29, NUMBER 3



Process Validation Guidance

Defining Regulatory Expectations

Interview with Dr. Jean-Louis Robert

Product Quality Lifecycle Implementation (PQLI)

Global Regulatory Framework

Barrier Isolation and RABS

Official sponsor of:

INTERPHEX™

ENGINEERING PHARMACEUTICAL INNOVATION

ISPE

www.ISPE.org

Dust Problem?

Go to where dust and fume pollution meet permanent solutions.

www.pharmadustcollectors.com

We make the toughest, best-built industrial dust collectors in the industry!

Visit www.farrapc.com today.

FARR®
Air Pollution Control

camfil FARR
Farr APC is a proud member of the Camfil Farr Group.
Visit www.camfilfarrapc.com for offices out of North America.

866-530-5474
Jonesboro, AR • email: filterman@farrapc.com

Adding value to enhance your bottom line.

CRB is a global provider of end-to-end solutions for life science and advanced technology companies. Our solutions deliver enhanced value, productivity and return on investment. Whether you are across town or across the pond, CRB's consulting, design and construction expertise will meet your R&D and manufacturing needs, while adding some black to your bottom line.

1.877.4CRBUSA

crbusa.com/ROI

Consulting Design Construction Commissioning Qualifications

EDITORIAL STAFF

Publications

Editor and Director of Publications
Gloria N. Hall

Publications Manager
Lynda D. Goldbach

Technical Writer
Rochelle Runas

Publications Coordinator
Amy Lecceardone

Sales

Director of International Sales
David J. Hall

Sales Coordinator
Valerie Adams

European Sales Manager
Christine Sainvil

PHARMACEUTICAL ENGINEERING® (ISSN: 0273-8139) is published bimonthly by ISPE, 3109 W. Dr. Martin Luther King Jr. Blvd., Suite 250, Tampa, Florida 33607, USA. Telephone +1-813-960-2105. Fax +1-813-264-2816. Periodicals postage paid at Tampa, Florida, USA.

BPA INTERNATIONAL

Subscriptions.
An annual subscription to PHARMACEUTICAL ENGINEERING is included in the membership of ISPE.

US Postmaster:
send change of address to Pharmaceutical Engineering, 3109 W. Dr. Martin Luther King Jr. Blvd., Suite 250, Tampa, Florida 33607.

Canada Postmaster:
send change of address information and blocks of undeliverable copies to PO Box 1051, Fort Erie, ON L2A 6C7. Canada Post Agreement Number 40041350.

ISPE HEADQUARTERS
3109 W. Dr. Martin Luther King Jr. Blvd.
Suite 250
Tampa, Florida 33607 USA
Tel +1-813-960-2105
Fax +1-813-264-2816

ISPE ASIA PACIFIC OFFICE
73 Bukit Timah Road
#04-01 Rex House
Singapore 229832
Tel +65-6496-5502
Fax +65-6336-6449

ISPE CHINA OFFICE
Suite 2302, Wise Logic International Center
No. 66 North Shan Xi Road
Shanghai 200041, China
Tel +86-21-5116-0265
Fax +86-21-5116-0260

ISPE EUROPEAN OFFICE
Avenue de Tervueren, 300
1150 Brussels, Belgium
Tel +32-2-743-4422
Fax +32-2-743-1550

www.ISPE.org

The Global Information Source for Pharmaceutical Science and Manufacturing Professionals

PHARMACEUTICAL ENGINEERING®

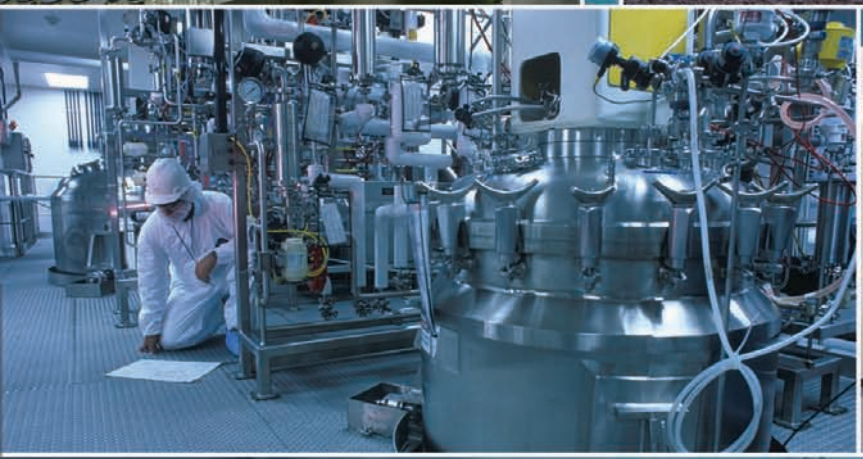
THE OFFICIAL MAGAZINE OF ISPE

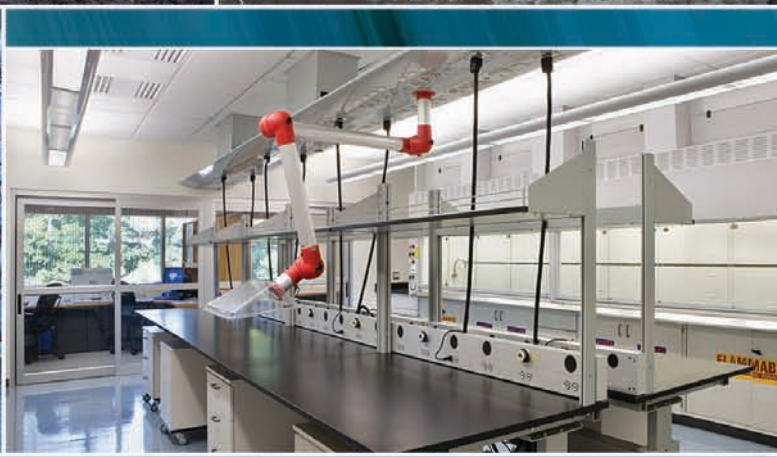
MAY/JUNE 2009 VOLUME 29, NUMBER 3

PARSONS

Integrated Solutions for the Global Life Sciences Industry

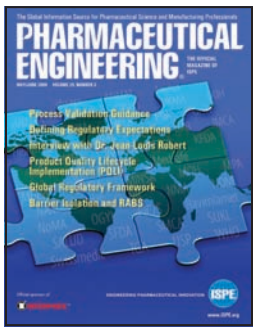
Engineering, Architecture, Procurement,
Program and Construction Management, Validation





www.parsons.com 1.800.555.0532 LifeSciences@parsons.com

Table of Contents



The Global Information Source for Pharmaceutical Science and Manufacturing Professionals

PHARMACEUTICAL ENGINEERING®

THE OFFICIAL MAGAZINE OF ISPE

MAY/JUNE 2009 VOLUME 29, NUMBER 3

Cover Design

Lynda Goldbach, ISPE Publications Manager

Current Issue/Theme

MAY/JUNE 2009
Regulatory - PQLI

Next Issue/Theme

JULY/AUGUST 2009
Utilities
Publishes 21 July 2009

Articles

8 **The FDA's Draft Process Validation Guidance – A Perspective from Industry**
by Nuala Calnan, Alice Redmond, and Stan O'Neill

18 **The Draft Process Validation Guidance – A Perspective from the FDA**
Q&A between industry and FDA from an ISPE Webinar on the draft guidance

24 **A Comparison of the FDA's Draft Process Validation Guidance and ASTM E2500**
by Robert E. Chew, PE

32 **Industry Interview Series:**
Dr. Jean-Louis Robert, Head of Luxembourg's Laboratoire National de Santé, Service du Contrôle des Medicaments
by Dr. John C. Berridge

36 **PQLI® – What is it?**
by Dr. John C. Berridge

40 **Global Regulatory Framework Overview: US FDA, EMEA, PIC/S, and ICH**
by Dr. Kate McCormick

50 **Barrier Isolation History and Trends – 2008 Final Data**
by Jack Lysfjord and Michael Porter

56 **Restricted Access Barrier System (RABS) History and Trends – 2007 Final Data**
by Jack Lysfjord and Michael Porter

Departments

60 **ISPE Update**

US FDA Speakers Figure Prominently at ISPE's 2009 Washington Conference

ISPE Korea Affiliate in Development

INTERPHEX Keynote Message: Industry Needs to Reinvent Itself

JPI Features Article on PQLI Legacy Products

ISPE Brussels Conference Highlights

64 **Classified Advertising**

66 **Advertiser's Index**

ISPE
ENGINEERING PHARMACEUTICAL INNOVATION

On-Line Exclusive Articles

China State Food and Drug Administration (SFDA) – Responsibilities, Internal Structure, and Affiliated Organizations by Jason Tang

...and Global Regulatory News

visit www.ISPE.org/PharmaceuticalEngineering

No matter what they throw at you, we've got you covered.

FDA

YOU HAVE TO COMPLY!

FORM 483

GLP/GMP

ISO STANDARDS

ANNUAL REPORTS

WARNING LETTER

ADVERSE EVENTS REPORTING

21 CFR PART 11

PRESCRIPTION DRUG MARKETING ACT

ICH GCP AUDITS

CONSENT DECREE

QSR AUDITS

CLINICAL MONITORING

TRACEABILITY DOCUMENTATION

QPHARMA

22 South Street • Morristown, NJ 07960 • **888-742-7620** • **info@qpharmacorp.com** • **www.qpharmacorp.com**

This article provides an overview of the draft guidance, the key changes in relation to the 1987 guidance, and reviews its potential impact on the current industry approaches to science- and risk-based design and qualification activities which support the process validation program.

The FDA's Draft Process Validation Guidance – A Perspective from Industry

by Nuala Calnan, Alice Redmond, and Stan O'Neill

Abstract

The long anticipated draft of the FDA's *Guidance for Industry* on Process Validation should be welcomed for the clarity of its integrated three stage lifecycle process, its emphasis on the need for effective scientific knowledge led programs, and the elimination of the "Three Golden Batches" concept.

Introduction

In November 2008, the FDA published the long anticipated draft of its *Guidance for Industry* on "Process Validation: General Principles and Practices." This draft, which has just completed its public comment period, will replace the FDA's 1987 "Guideline on General Principles of Process Validation" when finalized and represents the FDA's current thinking in regard to process validation. It sets out the approaches that the FDA consider to be appropriate elements of process validation for the manufacture of human and veterinary drugs, including biologicals and APIs. No specific mention is made within the scope to investigational medicinal products or medical devices, for which CDRH has published its own guidance through the Global Harmonization Task Force.

This article provides an overview of the draft guidance, the key changes in relation to the 1987 guidance, and reviews its potential impact on the current industry approaches to science- and risk-based design and qualification activities which support the process validation program.

Basic Principles of Quality Assurance

Effective **Process Validation** contributes significantly to assuring drug quality.

The basic principle of **Quality Assurance** is that a drug should be produced that **is fit for its intended use**; this principle incorporates the understanding that the following conditions exist:

- Quality, safety, and efficacy are designed or *built* into the product.
- Quality *cannot be adequately assured* merely by in-process and finished-product inspection or testing.
- Each step of a manufacturing process is controlled to assure that the finished product meets all design characteristics and quality attributes including specifications.

Ref: Guidance for Industry Process Validation: General Principles and Practices (Nov 2008).

The Lifecycle Approach

The guidance states at the outset that it has been written to promote "*modern manufacturing principles, process improvement, innovation, and sound science*" and is significantly aligned with the ***Product Lifecycle Approach*** described in the ICH Guidance Q8 (R1), Q9, and Q10[1] and the Quality by Design (QbD) initiative. This lifecycle approach emphasizes the importance of the links between the following:

1. product and process design and development
2. qualification of the commercial manufacturing equipment and process
3. maintenance of the process in a state of control during routine commercial production

Continued on page 10.

DeltaV Batch.

The perfect cup. Every time.

Easy.

Emerson understands your need to quickly respond to varying customer requirements. That's why we designed DeltaV Batch to give you the robust, repeatable performance that lets you assure your customers of a perfect, on-spec batch. First time. Every time. Easy.

From seamless integration with your enterprise planning and manufacturing execution systems to modular, class-based configuration and integrated change management, DeltaV Batch simplifies your batch operations.

Enabling agile manufacturing has never been easier. So, grab yourself a fresh cup and visit: **EasyDeltaV.com/Batch**

DeltaV™

EMERSON.™
Process Management

EMERSON. CONSIDER IT SOLVED.™

Three Stages of Process Validation

Process validation involves a series of activities taking place over the lifecycle of the product and process.

Stage 1 – Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
Stage 2 – Process Qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.
Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

Ref: Guidance for Industry Process Validation: General Principles and Practices (Nov 2008).

One of the key messages from this draft is that validation of the process is not a "one off" event, but represents an ongoing continuum of scientific knowledge development and ongoing assurance. There is a real emphasis throughout the draft on the importance of acquiring this knowledge about the process from the early process design stage right throughout commercial manufacture, which is a significant departure from the convention of (essentially) testing the process outputs. Success relies on the establishment of a comprehensive science-based process design, which focuses on understanding the sources of variability in achieving process understanding and recognizes that more knowledge will be gained during product commercialization. The draft emphasizes that the key to this success will lie in an organizations proficiency "in the collection and evaluation of information and data about the performance of the process," and outlines specific guidance relating to the use of quantitative statistical methods to enhance understanding of process performance.

From this, the guidance defines Process Validation activities in three stages identified in Figure 1.

Key tenets of the lifecycle approach outlined are:

- A manufacturer should have gained a high degree of assurance in the performance of the manufacturing process before any batch from the process is commercially distributed for use by consumers.
- This assurance should be obtained from objective information and data from laboratory, pilot, and/or commercial scale studies – this implies a need for greater scrutiny of process performance during the early stages of commercial manufacture.
- A successful validation program depends upon the skilled interpretation of the information and knowledge gained from product and process development regarding sources of variation, its impacts, and the associated risks.
- This knowledge and understanding is cited as the basis for establishing the appropriate control strategy for the manufacturing process.
- The product and process design and development information is then used to develop the approach to process validation, and the scientific knowledge is verified by testing (in-process, release, characterization) of each significant step of the commercial manufacture process.
- The significant emphasis in the lifecycle is on maintaining the process in a state of control over the life of the process, which will require ongoing data analysis of both intra-batch and inter-batch variability, and appropriate provisions to address deviations and nonconforming data.
- It emphasizes the importance of both QA professionals and line operators in providing feedback for continued process verification.
- Not surprisingly, the guidance focuses on the importance of demonstrating, documenting, and utilizing process understanding in designing effective validation programs. It provides a strong lead in acknowledging that qualification programs devoid of process understanding will not guarantee the assurance of quality required.

Significant Recommendations

The main body of the guidance is provided under section IV *Recommendations,* where very useful general considerations on the three stages of process validation and their associated activities are outlined.

This is where we see the most significant alignment with current industry thinking for implementation of science- and risk-based lifecycle approaches and where the most significant departures from the prescriptive approaches of the 1987 guidance are noted.

Under **"General Considerations for Process Validation,"** it emphasizes the importance of making the entire process validation program more effective and efficient through the following:

- good project management
- robust scientific knowledge collection, management, and archiving
- uniform collection and assessment of information methods
- reducing the burden of redundant information gathering
- use of an integrated team approach

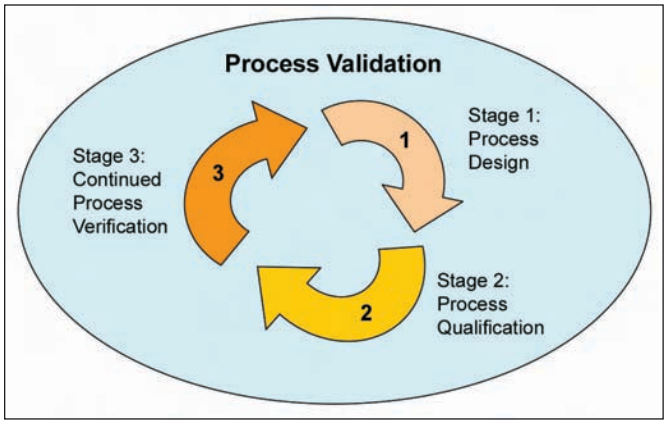
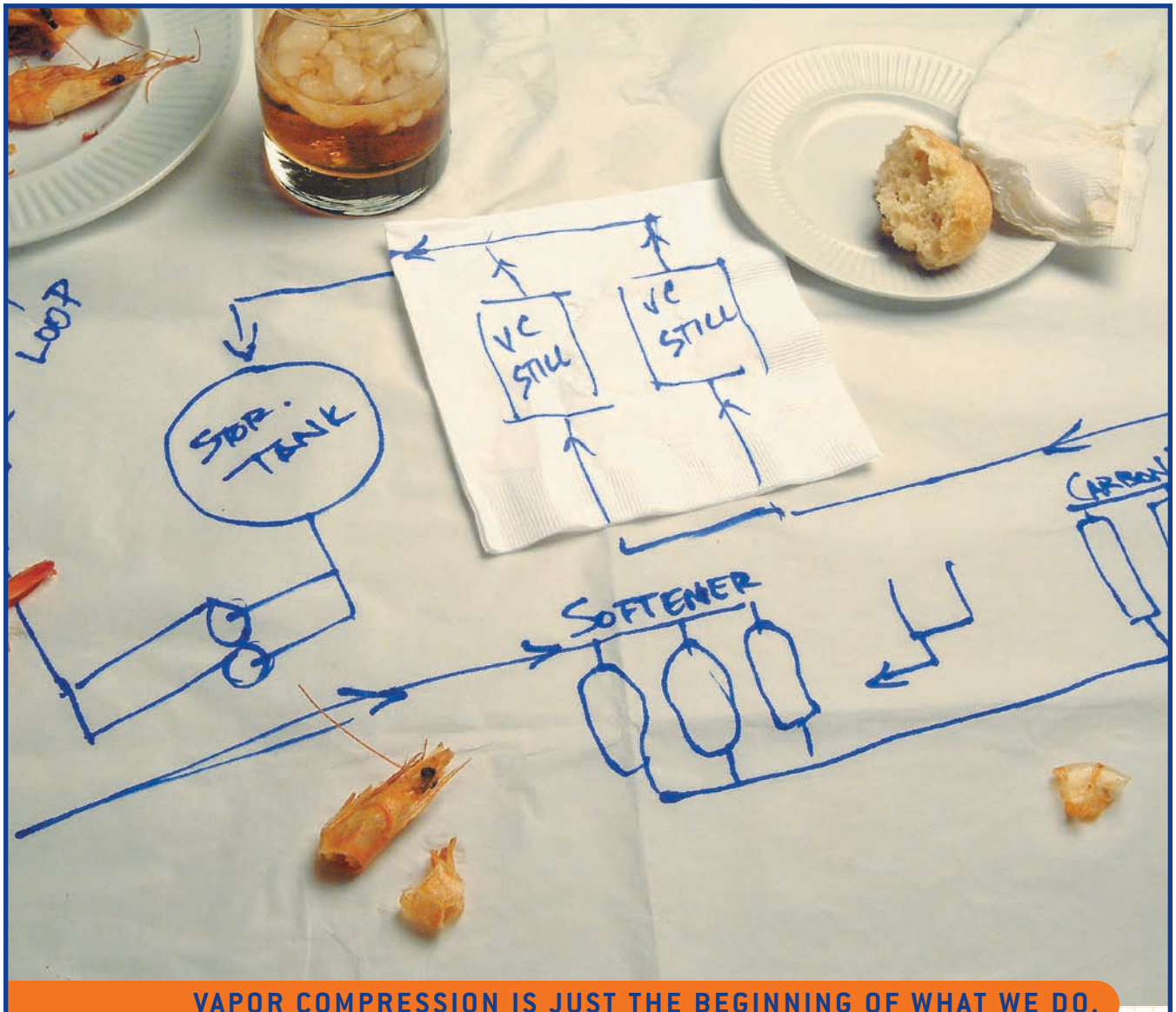


Figure 1. Process validation lifecycle activities shown in three stages.

Continued on page 12.



VAPOR COMPRESSION IS JUST THE BEGINNING OF WHAT WE DO.

Innovative Solutions For Purified And WFI-Grade Water And Pure Steam.

It was a big idea that simply got bigger. Today, MECO has grown to provide expert guidance and customized solutions for every phase of water and Pure Steam generation. Whether you need a particular product, a specialized service or an entire water plant designed and built from scratch, MECO delivers. To see for yourself, visit mecobiopharm.com or call 1-800-421-1798.

MECO

MECO NO BOUNDARIES PROMISE

PEOPLE | PRODUCTS | SERVICE

US _ UK _ Singapore _ UAE _ 800-421-1798 _ mecobiopharm.com

12505 Reed Road, Suite 100, Sugar Land, TX 77478

Key Definition: Process Validation (PV)

*"The collection and evaluation of data, from the process design stage throughout production, which establishes **scientific evidence** that a process is capable of consistently delivering quality products"*

Ref: Guidance for Industry Process Validation: General Principles and Practices (Nov 2008).

- appropriately documented Project Plans
- the support of senior management
- statistical assessment of data

The draft recommends the "integrated team approach" as presented in the FDA's 2006 guidance entitled, "Quality Systems Approach to Pharmaceutical Current Manufacturing Principles," involving expertise from a variety of disciplines, including process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance. Furthermore, both here and throughout the document, it emphasizes the need for effective and efficient programs and supports the move away from overly bureaucratic traditional qualification practices and in doing so provides good alignment with the key principles of the recent ASTM standard E2500-07.[2]

In "Specific Stages and Activities of Process Validation in the Product Lifecycle," the guidance gives specific direction on each of the three stages of process validation.

Stage 1: Process Design

The stated goal of this stage is to *"design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its Critical Quality Attributes (CQAs)."* The guidance again makes reference to ICH Q10, Pharmaceutical Quality Systems, and draws some distinctions around the varying levels of controls required related to the product development lifecycle activities.

The focus of this stage is on developing methods and competencies for building and capturing process knowledge and understanding and in using this scientific knowledge as the basis for establishing an approach to effective process control. It states that the *"Design of Experiment (DOE) studies can help develop process knowledge by revealing relationships, including multi-factorial interactions, between the variable inputs (e.g., component characteristics or processing parameters) and the resulting outputs (e.g., in-process material, intermediates, or the final product)."* Risk analysis tools can be used to minimize the total number of experiments conducted while maximizing knowledge gained. The results of the DOE studies should be used to establish ranges of incoming component quality, equipment parameters, and in process material quality attributes.

The draft draws attention to the recent advances with Process Analytical Technology (PAT), which may be used for real time analysis, facilitating control loops to adjust the processing conditions so that the process output remains constant and reproducible. However, it does indicate that in the case of PAT, the approach to process qualification will be different from that for other process designs by focusing on the qualification of the measurement system and control loop.

Significantly, by grouping the recommendations for product and process design together in this stage, it further endorses an integrated approach. Within this integrated approach, while it acknowledges that the full spectrum of input variability typical of the commercial production is not generally known at this stage, it directly recommends that the team responsible for process design take early consideration of the functionality and limitations of commercial manufacturing equipment by utilizing their knowledge about measurement systems in a production setting, contributions to process variability from different raw materials or component lots, production operators or environmental conditions. This ethos will no doubt be welcomed by many involved in the start up of regulated commercial manufacturing facilities who have dealt with the challenges posed when this early integration of commercial production and process design has not been successful.

Stage 2: Process Qualification

This stage of the process validation lifecycle is undoubtedly going to generate the most comment and perhaps lead to some initial confusion, due to its use and definition of terminology relating to *Process* and *Performance* qualification.

The stated goal of this key stage is that *"the process design is confirmed as being capable of reproducible commercial manufacture."* The guidance further divides this stage into the following two elements:

1. design of the facility and qualification of the equipment and utilities
2. Performance Qualification (PQ)

Stage 2-1: Design of the Facility and Qualification of Utilities and Equipment

This section of the guidance opens with a welcome reference to the essential role that proper facility design and commissioning play in the start-up of a facility and cites them as prerequisites to the commencement of PQ.

Most significantly, the guidance gives a key definition for qualification as shown below:

The draft guidance states that qualification of utilities and equipment generally includes the following activities:

Key Definition: Qualification

"Activities undertaken to demonstrate that utilities and pieces of equipment are suitable for their intended use and perform properly is referred to in this guidance as qualification"

Ref: Guidance for Industry Process Validation: General Principles and Practices (Nov 2008).

Continued on page 14.

ELETTRACQUA

pure water technologies

SINCE 1966

PHARMACEUTICAL WATER SYSTEMS

DOUBLE PASS REVERSE OSMOSIS HIGH TEMPERATURE SANITIZATION

DESIGN AND CONSTRUCTION OF PURIFIED WATER PACKAGES ♦ DOUBLE PASS REVERSE OSMOSIS ♦ R.O. + ELECTRODEIONIZATION HOT WATER SANITIZABLE ♦ ULTRAFILTRATION ♦ MULTIPLE - EFFECT DISTILLATION UNITS ♦ PURE STEAM GENERATORS ♦ STORAGE AND DISTRIBUTION LOOP ♦ COMPLETE TURN KEY PROJECTS ♦ VALIDATIONS IQ, OQ

www.elettracqua.com

visit us at
ACHEMA 2009
Frankfurt am Main/Germany
11.–15. 5. 2009
hall 4.1 - stand L20/L22

- selecting utilities and equipment based on whether they are appropriate for their specific use
- verifying that the utility system and equipment are built/installed in compliance with the design specifications and operate in accordance with the process requirements in all anticipated operating ranges for routine production
- challenging the equipment or system functions while under loads comparable to that expected during routine production
- performance of interventions, stoppage, and start-up as is expected during routine production

The guidance requires that these *qualification* activities are covered either under an individual plan or as part of an overall project plan. In line with the ICH Q9, Quality Risk Management guidance, the plan should consider the use of risk management to prioritize certain activities and to identify the appropriate level of effort for both the performance and the documentation of these qualification activities.

Finally, it confirms the requirement for the *qualification* activities to be documented in a report with conclusions that specifically address the criteria set out in the plan. It is important to note this draft's expectation that the quality control unit must review and approve both the qualification plan and the report. There is divergence here with the recently published ASTM E2500-07[2] standard, which seeks Quality Unit preapproval of the qualification acceptance criteria rather than the plan, but concurs on the Quality Unit post approval of the qualification report.

Stage 2-2: Performance Qualification (PQ)

Performance Qualification (PQ) is the phrase used to described the second element of the overall process qualification and combines the actual qualified facility, utilities, and commercial manufacturing process equipment with the trained personnel using cGMP compliant control procedures (SOPs), and all raw materials and components necessary to produce commercial batches.

The use of the phrase Performance Qualification (PQ) in the context of producing commercial batches may present divergence from what is widely understood to be within the scope of a "traditional" PQ, which currently focuses on equipment and process performance for clean utilities, cleaning, and sterilization processes. In the 1987 guide, this was described as *Process Performance Qualification* and was distinguished from that which was referred to as *Product Performance Qualification*. This draft combines the two efforts within this stage in order to achieve the stated goal of overall *Performance Qualification (PQ)* which is to *"confirm the process design and demonstrate that the commercial manufacturing process performs as expected."*

Success at this stage is cited as an important milestone in the product lifecycle and must be completed before a manufacturer commences commercial distribution of the drug product.

The draft requires that the design of the PQ study should ensure that:

- The manufacturing conditions set for the PQ are established based on the cumulative data from all relevant studies (e.g., designed experiments; laboratory, pilot, and commercial batches).
- Objective measures (e.g., statistical metrics) are used to evaluate the outputs and justify that adequate assurance has been achieved.
- Greater scrutiny of process performance is undertaken during PQ through the use of enhanced levels of sampling and testing. This enhanced level of monitoring and testing should be capable of confirming uniform product quality is achieved throughout the batch during processing.

It will be important to understand and assess the impact of these expectations relating to PQ early in the overall lifecycle as they may affect process development activities, system design, equipment selection, or team selection considerations and will certainly influence the development of methods and procedures.

In relation to the number of PQ batches required, to date product PQ was typically followed by the traditional "three PV batches." Now no fixed number of new PQ batches are prescribed and manufacturers must provide justification for any rationale used in asserting that assurance has been achieved. However, it is noted that the words "commercial batches" are used, which would suggest the use of more than one batch.

Furthermore, it is important to note the expectation that the greater scrutiny accompanied by the enhanced level of sampling undertaken during the PQ batches should continue initially into the continued process verification stage.

Of particular note in the document is the recommendation that the PQ lots should be manufactured under normal conditions. Thus, a matrix approach with extremes of operating conditions is not expected for this phase of validation.

The guidance provides specific recommendations on the format and content of the PQ protocol and the report including as follows:

- manufacturing conditions, such as operating parameters, process limits, and raw materials inputs are documented
- details of the data to be collected, including when and how it is evaluated
- details of the in-process, release, and characterization tests to be performed, as well as the acceptance criteria for each significant step
- the sampling plan, including sampling points, the number of samples, and the frequency of sampling for each unit operation, based on statistical confidence incorporating risk analysis
- criteria showing the processes consistently produce quality batches, including a description of the statistical methods used to define both intra-batch and inter-batch variability, and provisions to address deviations and nonconforming data
- design of facilities and qualification of utilities and equip-

1987 PV Guidance	2008 Draft
Defines validation as "establishing documented evidence"	Defines validation in terms of "establishing scientific evidence"
Principles of quality assurance wording revision from "cannot be inspected or tested into the finished product"	to "cannot be adequately assured merely by in-process and finished product inspection or testing"
Principles of quality assurance wording revision from "designed and built into the product"	to "is designed or built"
Wording revision from "maximize the probability that"	to "is controlled to assure"
	Introduction of "integrated team approach"
	Introduction of "product lifecycle" concept
	exclusion of "revalidation" and "retrospective process validation"
	Introduction of Process Analytical Technology (PAT) concepts for PV
	Introduction of "root cause" (e.g., review of customer complaints and impact on process)
	Removes validation information for medical devices
	Emphasizes Science Based Knowledge development
	Emphasizes the use of qualitative statistical methods to monitor, evaluate and justify assurance of process performance

Table A. Key changes between 1987 PV Guidance and 2008 Draft.

ment, training, and verification of source materials
- validation status of analytical methods used to measure the process, materials, and product
- review and approval by the appropriate department and the quality unit

Finally, the draft elaborates on the opportunities presented for manufacturers utilizing PAT systems to support activities undertaken in the next stage.

Stage 3: Continued Process Verification

The stated goal of the third process validation stage is to *"continually assure that the process remains in a state of control (the validated state) during commercial manufacture."* This will require robust systems for detecting unplanned departures (drift) from the designed process, and there is a strong emphasis on the use of statistically trended data, which is reviewed in a timely manner by trained personnel, such as statisticians or persons with adequate training in statistical process control techniques.

The development of a Data Collection Plan is recommend ensuring that the information collected can verify that the critical quality attributes are being controlled throughout the process.

This production data also should evaluate process stability and capability and the scrutiny should include both intra-batch as well as inter-batch variation. The quality unit should evaluate this data, discuss possible trends or drifts in the process, and coordinate any correction or follow-up actions with production personnel.

As referred to previously, the draft recommends that the enhanced monitoring and/or sampling initially established during the process qualification stage continue until sufficient data is available to generate significant variability estimates and justification, using statistical metrics, is available to support their relaxation.

It is noted that data gathered during this stage may identify ways to improve and/or optimize the process and appropriate procedures to control and manage these changes must be in

Concludes on page 16.

place. It highlights that maintenance of the facility, utilities, and equipment is another important aspect of ensuring that a process remains in control. While the document discusses the use of continued process verification to identify variability and improve the process, no mention is made to the possible implications on already commercialized batches.

Finally, it states a fundamental tenet that following the scientific based approach requires that information transparency and accessibility are essential so that organizational units responsible for the process can make informed, science-based decisions that ultimately support the ongoing commercial release of a product.

Conclusion

It is the opinion of the authors that this guide will be welcomed for many reasons, primarily for the clarity and simplicity of the integrated three stage lifecycle process, but also for the emphasis on the need for effective and efficient science-based programs, which seek to reduce unnecessary duplication in activities through the application of product and process knowledge throughout the lifecycle.

From a facility, utility, and equipment qualification perspective the welcomed avoidance of traditional, prescriptive terminology such as DQ, IQ, and OQ offer teams real opportunities to look behind the prepared templates and design and execute qualification and validation programs which are not only valid, but valuable to the ongoing operation and continuous improvement. There is only one minor exception to this relating to an external cross reference in the introduction to the very prescriptive validation approach for APIs found in the ICH Q7A guidance. This is likely to add confusion rather than clarity and which hopefully will be dealt with through the public comment phase.

Upon first review, this draft in itself does not appear to have any new implications for the preparation and submission of regulatory filings.

However, for many organizations, aligning this FDA process validation guidance with the current EMEA legislative requirements and recommendations for process validation would be very beneficial.[3]

Finally, from an ISPE Technical Documents perspective, due to the revised use of terminology and the welcome step back from prescriptive qualification practices, final publication of this guidance will provide an opportunity to review several current ISPE Guidance documents for alignment. This will impact both the Baseline® Pharmaceutical Engineering Guides series and Good Practices Guide series, many of which are already under revision for alignment with recent ICH guidance.

References

1. See the FDA/International Conference on Harmonisation (ICH) guidance for industry:
   a. Q8 Pharmaceutical Development
   b. Q9 Quality Risk Management
   c. Q10 Pharmaceutical Quality Systems
2. ASTM E2500-07: Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment, July 2007.
3. Notes for Guidance on Process Validation; CPMP/QWP/848/96, EMEA/CVMP/598/99 September 2001.

About the Authors

Nuala Calnan is a Principal Consultant with PM Group, Ireland and has more than 17 years of experience in the pharmaceutical industry. Currently, she is a member of the ISPE International Board of Directors and was a member of the Author Task Team which produced the recent ASTM E2500-07 International Standard. Calnan also is a member of the document development task team currently writing the *ISPE Baseline Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment*. She graduated in 1991 with a BSc in engineering (BSc Eng) and achieved her MBA in 2002. She is a regular contributor at ISPE conferences. She can be reached by telephone: 353-14040700 or by email: nuala.calnan@pmg.ie.

PM Group, Kilakee House, Belgard Square, Tallaght, Dublin 24, Ireland.

Alice Redmond is CQ Technical Director with PM Group, has more than 20 years of experience in the R&D, pharmaceutical (API, formulation fill, solid dosage), and biotechnology industry. She graduated with a BSc in biotechnology in 1987, a PhD in biotechnology in 1991 and a MBs in 2001. Current responsibilities include oversight of regulatory compliance, GEP, quality, commissioning, qualification and validation strategies on a corporate level for PM Group. Redmond is an active member of ISPE and PDA. She co-chaired and presented at the ISPE GEP ICQ Conference in Copenhagen in 2006, and the Singapore ISPE Conference in July 2008. She can be contacted by telephone: 353-214358922 or by email: alice.redmond@pmg.ie.

PM Limited, Loughmahon Technology Park, Blackrock, Cork, Ireland.

Stan O'Neill is the Managing Director of the Compliance Group. After qualifying as a pharmacist, he spent more than five years working in the pharmaceutical industry in Regulatory Affairs, marketing, and Quality Assurance (QP), and then joined the Irish Medicines Board (IMB) for a period of 10 years. In his capacity as a Senior Inspector, he performed GMP inspections throughout the world, represented Ireland at European level for the negotiation of standards of inspection for medicinal products, and trained Inspectors at Irish, European, and International levels. He can be contacted by telephone: 353-866032297 or by email: stanoneill@compliancegroup.eu

The Compliance Group, 22 Earlsfort Terrace, Dublin 2, Ireland.

Expertise right down the line

Glatt granulation line

Perfected manufacturing of high density granules in a single production system is one example of Glatt's core competence.

As always, state-of-the-art: Glatt's vertical granulator in combination with Glatt's efficient fluid-bed dryer is a proven technology for manufacturing high density wet granules. Modular configuration is available with the addition of wet and dry sieves. Granulation lines from Glatt incorporate 2-bar venting or are available with our unique closed 12-bar safety design. Glatt has the perfect solution for every application.

- Clear advantages due to the maximum safety design, optimum handling and minimum space requirements
- Horizontal or vertical product flow configurations available
- No intermediate explosion safety devices required for the entire granulation line thanks to the 12-bar safety system
- SC SuperClean®: fully automated, CIP cleaning system with validation
- Intelligent multipanel control design
- Optional through-the-wall design

Fluid Bed Systems

Vertical Granulators

Product Handling

Pan Coaters

Engineering

Services

Glatt Air Techniques Inc.
20 Spear Road
Ramsey, NJ 07446 / USA
Phone: +1 201 8 25 87 00
Fax: +1 201 8 25 03 89
eMail: info@glattair.com

Glatt GmbH Process Technology
Werner-Glatt-Straße 1
79589 Binzen / Germany
Phone: +49 7621 6 64 0
Fax: +49 7621 6 47 23
eMail: info@glatt.com

www.glatt.com

Glatt®

PE / 1SPE – MAY / JUNE 2009 – NEUBERGER.DESIGN

This article presents the questions and answers from a recent ISPE Webinar focused on the FDA's draft process validation guidance.

The Draft Process Validation Guidance – A Perspective from the FDA

Introduction

In January 2009 Grace McNally of the US FDA provided a first time public view and understanding on the new draft *Guidance for Industry – Process Validation* in a live ISPE Webinar. Paul D'Eramo, Executive Director, Johnson & Johnson, hosted a question and answer session which gave attendees the chance to submit their questions and have them directly answered by McNally. The following is a transcript of some of the highlights of that Q&A session:

Q Do we have any idea on when it might get finalized?

A Once we get the comments in we'll have to empanel a group of experts to evaluate them, make some decisions, write responses, and adopt suggestions if appropriate or not. I can't tell you exactly how long that process will take but it's certainly our intention to get that done and get a final published this year, 2009.

Q Did you discuss this draft with other regulatory bodies such as in Europe, to see what their reaction might be in regards to harmonizing some of their documents?

A No, this was an FDA effort only and it did not involve other regulatory agencies. Certainly, it's available to them. I've been to conferences where representatives from other regulatory bodies have asked about it, so they are aware that it was in draft. Of course, it's on the Web and it's available for everybody to take a look at and comment on.

Q It's clear in the document you've referenced Q8, Q9, and Q10. It's not as clear as how this relates to Q7, especially because there are sections in Q7 that discuss validation. So should we defer to that?

A Yes, Q7A has a very prescriptive specific section about validation. That is the standard for APIs. If there appears to be any conflict between that and this guidance, I would certainly ask that you submit those comments to us and we will consider them as we revise the guidance for final.

Q When you implement this, is there a plan for how you will be training the FDA investigators to make sure everybody's consistent?

A Yes, that's a very good question. We haven't done that in a formal comprehensive way. We have the basic drug school or courses geared toward our pharmaceutical inspectorate. Myself and others involved in this working group have given talks about this new guidance – it wasn't published because we weren't distributing it at that point – and the concepts in it, discussing the principles and how they should be thinking about process validation, which isn't terribly different than the thinking we had under the 1987 guidelines. A careful reading of the 1987 guidelines is very revealing. It is not fundamentally different in its basic principles.

But yes, the investigative staff will need to be trained and we will be developing a formal training program. Certainly this is just a draft and there may be revisions, so we are not prepared to do that quite yet until we have the final. As far as the implementation phase, it's important to remember that this is a guidance, it's not a regulation. These are recommendations. This is the current thinking about what we believe are useful practices for process validation in this day and time. So an implementation phase doesn't really apply to this guidance.

Q How does this guide relate to the aseptic processing guide? Does that processing guide take precedent for sterile products?

Continued on page 20.

In safe hands

Containment Solutions for the Pharmaceutical & Biotech Industries

- Barrier Isolation Systems
- Downflow Containment Booths
- High Containment Screens
- Pack Off and Process Equipment
- Kilo Labs & Glassware Enclosures



howorth
air technology

For further information please contact us on
North America 502 968 2065
Rest of the World +44 (0) 1204 571131
info@howorthgroup.com www.howorthgroup.com

A Yes, that's a good point. The aseptic processing guide is as direct and prescriptive for that activity and that manufacturing operation. So if there is a guidance out there that specifically addresses a type of manufacturing activity, that is what you want to look at. This guidance is not intended to conflict with the aseptic processing guide or any of the guidances out there. I know in the biological realm there are specific guidances for viral clearance or other technical manufacturing aspects and those should be your primary reference.

Q Can you explain the major differences between the old guide and the new as it relates to existing (or legacy) products? For example, if we have to revalidate an existing product, should I use the new guideline or the old principles?

A Process validation is a lifecycle and if you're in a position of revalidating, for whatever reason... I would direct your attention to Stage 3. If you have an existing product in process and you're revalidating it, I would assume there's been some trigger for that. It would make sense to me that the trigger for that is information you gathered during what we're calling Stage 3, commercialization activities that you do under 211.180 (e), part of your periodic evaluation. (That information) brought to your attention something that needs to be changed or checked. So it would make sense at that point to incorporate the principles in this new guidance. And remember they're not that different. If I was to go back, and I do have the old guideline here in front of me, it also calls for a maintenance of a state of control.

So I would say good companies concerned about quality are going to use revalidation for whatever the impetus was... to adopt a modern view. As a company you also want to be philosophically congruent. If companies are embracing an attitude of continuous improvement it seems to me that that would permeate their thinking for all their product lines. Now, having said that I'm not saying if you have an old process that is performing well, and there's no indication, there's no quality indicator data that suggests to you something is amiss, I'm not suggesting that you run out and begin R&D all over for each of these product and process lines.

It would make sense to me that as part of your overall quality system, and certainly as part of the periodic evaluation of all product lines, that whatever your procedures dictate that you consider each of these products and processes as part of your periodic evaluation procedures. You can certainly take for example, you may want to consider some sort of risk analysis of each of your product lines and processes and see what can and should be done to improve them if that appears necessary, based our your data and evaluation. There's no move afoot on our part to send investigative teams out to go through a company's product line, find the five year old process that seems to be doing quite well and start digging into R&D records … that's not the goal and it won't be part of any action on the field's part.

But I would say to you as the company to think about your processes and product lines. You do and are required and certainly want to have in place these periodic evaluation procedures. So when an older and existing process comes up, my question then to you, is do you think you should apply these new principles. And they're really not that new actually. I would recommend that everybody who is concerned about this new guidance being different than the old should sit down with the new one and the old one and carefully read them.

Q Someone made the comment, it seems our industry lags somewhat in process monitoring/statistical process control. It is now clear that this is an expectation. Another asks, can you use Six Sigma concepts to rationalize process validation being in a state of control. Can you elaborate on that Continued Verification, Stage 3, the monitoring part, and how you foresee that?

A While it's true that references to statistical criteria and procedures are prominently featured in this guidance, I will say that that's not new … It's a topic that we need to shine light on and put on the table. It is my belief that it has been somewhat ignored as of late. Certainly it has to be wrestled with. It raises a lot of questions about how to do this.

But I would say it really is not new. I'm looking at the old guidance, second to last section. It's talking about testing, test data, and ...process monitoring. It says, "specific results on the other hand can be statistically analyzed and a determination can be made of what variance and data can be accepted." So those ideas have been around for a long time. In Stage 3, you can use Six Sigma. We're not going to prescribe what statistical tools to use and really we're just looking for a scientific basis and objective measures, and statistics are one of them.

In this day and age, I understand from many people in industry that there are a lot of good software packages out there and they can be very valuable. And even in Stage 2, you have limited data at that point and so the power of those analyses may not be as great because you have much more accumulative data in Stage 3, once you're making a lot of commercial batches … but they would be very useful. We're not going to dictate which statistical tools to use, but you as a company should select what works for you and be able to defend why it's scientific and objective.

Q Was a there a reason why risk analysis was not discussed in the document?

A Yes, we made a deliberate effort to not explore topics that have already been thoroughly covered in other guidelines or guidances. Risk management is thoroughly discussed in ICH Q9 and we've referenced it. But to avoid retread on already established concepts – we mention it and there is an expectation that risk analysis will be used throughout the lifecycle and all of the stages – felt it was not necessary to go into detail. That is expected, and

use the guidances available on it.

Q Will a glossary be added? There are terms such as process verification and product performance. Criticality is not really defined anywhere. Do you think you'll go back and put some of those terms into a glossary?

A A few thoughts on criticality. We actually in our earlier versions used the word critical throughout the document. The definition of criticality has been greatly debated. We've seen many definitions, whether individual companies prefer a definition, whether a regulatory body has a certain slant on their definition. In the interest of getting this guidance done, we did not put a glossary in because so many of the terms are debatable in terms of what they mean. Criticality, we took out of there and went back to our source document which is the GMP and chose to use the word "significant." So you'll see in those places that term instead of criticality.

But the comment about the glossary in general, there isn't a glossary. But if the comments we get back strongly suggest that that is indispensible or absolutely necessary in order to prevent confusion or make this guidance meaningful and useful then we'll take that into consideration.

And I should just say as an aside, there's no magic to the terminology that we chose to use for this guidance: Stage 1, Stage 2, Stage 3. They're just terms we chose and then laid out what they meant. That's something each of your individual companies probably do as well. Certainly there's value in everybody using and having the same meaning but to expect that to happen, I wouldn't bet money on it. I think the key about terminology is, whenever you get involved in a discussion with somebody, whether it's in an audit, or your collaborating on something, as long as that group understands what is meant by certain terms, then you can make progress and have a successful meeting or inspection, or move forward. But the glossary issue, I would say we will look at that in terms of the comments that we get back from everybody.

Q Is there value in executing PQ at ranges versus a target or should this be carried out in the development phase?

A That's a great question and that really speaks to the old guideline. In the old guideline you certainly get the impression that the boundary conditions (worst case challenges, edge of the operating parameters that have been established, whatever you want to call it, edge of operating limits) in the old guidance to me and my reading of it is that that's something you're going to do as your making commercial batches, this performance qualification stage or what we would call it, Stage 2. It seems to me that while that knowledge should be pursued, it would make sense that that would be in the Stage 1 arena, or I should at least say, it's not something you want to do when you're ultimately confirming your process design and working with product you intend to sell. I would agree with the inquiry statement that before you ready what you think is commercial product you've probably already explored that and have some understanding of what those limits are and what their impact is on the product quality and process. I agree that you would want to explore that up front.

Q Please elaborate on the following – "to have sufficient understanding of the commercial process, the manufacturer will need to consider the effects of scale; however, it is not typically necessary to explore the entire operating range at commercial scale if assurance can be provided by other data." Can you clarify what is sufficient understanding and what is the agency's thinking there and the same for scale? Does this need to be done at full scale batches?

A ...as far as sufficient data, there are certain words that the Agency will use, such as "appropriate" or "sufficient." Because it's going to differ from company to company and product to product… it's a judgment call that the manufacturer must make and then be able to explain why they feel this is adequate from a science perspective...

Concludes on page 22.

the key there, is people will talk in terms of how many commercial size batches do I have to make. The more important question is, having made these batches, however many there are, what is it that you're looking (for). That's the criteria. That's what you want to specify in your protocol, your plan. The real question is, but what about them, what are you doing with them, what is the data you're looking at, what is the information? Is it during processing, are you looking at the controls and the process parameters, how tight they are or not. Are you looking at attributes of the in-process material in the final product and what about it, are you going to do some analysis of that data. It's not about the number of batches, it's what data are you gleaning and how are you handling that data and what are your expectations.

Q Does the Continued Process Verification Program for a given drug product require formal protocol, similar in fashion to Performance Qualification? Should this data be collected, analyzed, summarized (and approved) by the QA – Validation Department?

A That's a very good question. I am not saying it's required but it makes rational sense. If you have a new product or process for which you don't have a lot of history and you don't have a similar product or process from which you could leverage information; I think that's one of the holes in the way things are operated right now. You have the pre-approval and post-approval and it goes from getting approval and launch to automatically, oversight is at routine levels. Well the routine levels may not be appropriate immediately.

To answer this person's question, it's not required, but I think it's an excellent idea, sort of a transition; things aren't on and off, like flipping a light switch. And I suspect companies don't just say it's a new process, and so now once it's approved we'll just treat it like the one that's been running for three years seamlessly. I think there is more oversight and appropriately so.

So under Stage 3 I can envision and would certainly recommend that you would have formal protocols, or at least a procedure. I don't want to say protocol because I don't want to give people the idea that this is what you have to do. But doesn't it make sense, if you're going to assess performance over time, to establish some criteria and some sort of procedure and then execute it, gather that data and do those analyses. And put numbers, I mean that's mainly where we're coming from, the statistics that you see in this new guidance are "objective measures," I think it maybe only says it once in there. But if you're going to assert that you have confidence in this unit operation, this process overall, this particular attribute, can you put a number on it. I think more and more today you can if you use the right tools.

Confidence intervals, how sure am I about this data point or this statistical metric I just calculated. How confident am I. It's going to depend on sample size, it's going to depend on a lot of things. But you can put a label on how confident you are on some of your data … I think this inquirer's insight is a fine one and makes sense. Again, Stage 3, if you're trying to maintain things in a state of control you want to be able to measure what it's doing, what is that process doing over time. It's really the essence of that 211.180 (e), Periodic Evaluation, when you say you're doing a Periodic Evaluation, what tools are you employing to do that. So really what the inquirer is getting at is what tools do we want to devise to do our Periodic Evaluation. I think it's a great idea.

Q You purposely did not use the number three in batches in the document, but there are a few questions asking if it would be appropriate to mention a minimum number?

A Here's the key word you have to think about. You have to demonstrate reproducibility. As far as a minimum number, again it's not the number of batches, it's what is the data. That's the key criteria that you're looking at, and how are you going to analyze that data using what tools. You have two considerations, the product attributes, and you have the process parameters and the ability to control them. So any criteria needs to account for both of those in some cogent, appropriate manner that I really think will differ from product to product and process to process. The agency isn't going to dictate that. As far as number ... there is this element of reproducibility, so right off the bat you know you've got to have more than one. And when I say one I don't mean one batch. I mean, I'd rather say data point, or for whatever the data points that are important or for whatever the attributes or parameters are important, reproducibility is an element that needs to be demonstrated.

Q Why doesn't the guide talk about revalidation?

A We didn't use "revalidation" because really Stage 3, the output of those monitoring activities, is going to give you the impetus to revisit potentially design or revisit Stage 2. So revalidation is really a function of what you find in Stage 3. It's covered in concept, we just didn't use the word. It's something Stage 3 will dictate what you need to do.

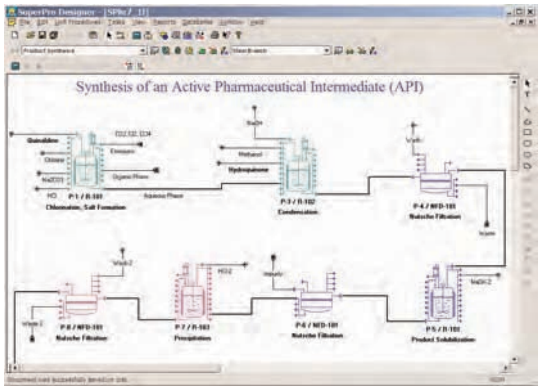
Q Can you please comment on the responsibilities of manufacturers of record and contract manufacturers? Who's responsible for the validation?

A Ultimately the manufacturer or the company's name that's on the label is responsible. Having said that, it's impossible for the contract manufacturer not to be involved. I know that there are these quality agreements that the contract manufacturer and the actual manufacturer of record will negotiate and the responsibilities should be laid out in these quality agreements. So there are special considerations. And that's very prevalent. There are lots of contract manufacturers even within one company so that has to be worked out and transferred, whether to a site in India or in the US... Both parties are going to have some responsibility because they will each be inspected on their own merit; they are registered drug companies. If you're responsible for transfer of a process to another location, that needs to be one of your primary concerns in getting those responsibilities laid out and understood by all parties.

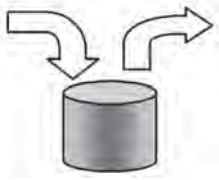
Intelligen Suite

The Market-Leading Engineering Suite for Modeling, Evaluation, Scheduling, and Debottlenecking of Single & Multi-Product Facilities

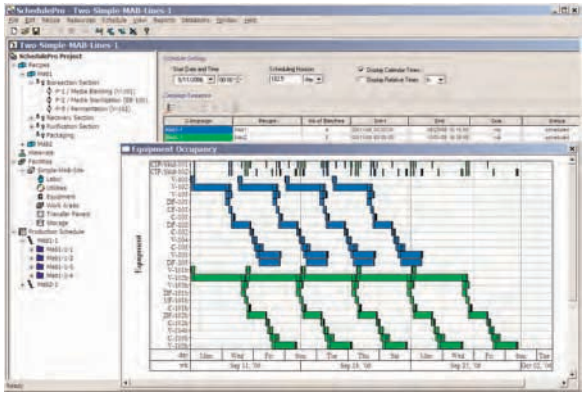
SuperPro



Use SuperPro Designer to model, evaluate, and debottleneck batch and continuous processes

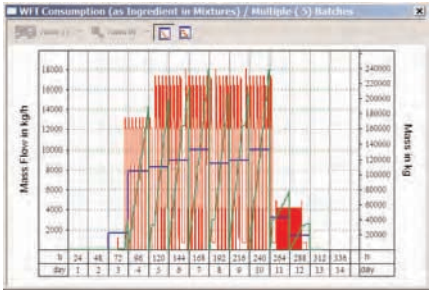


SchedulePro

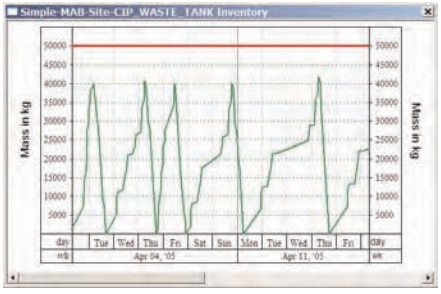


Switch to SchedulePro to schedule, model, and debottleneck multi-product facilities

Tracking of equipment occupancy in multi-product facilities



Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Inventory tracking for raw materials, intermediates, products, and wastes

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of biochemical, specialty chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 400 companies and 500 universities around the world (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile finite capacity scheduling tool that generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of facilities, equipment, resources and work areas. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size utilities for batch plants, identify equipment requirements, reduce cycle times, and debottleneck facilities.

Visit our website to download detailed product literature and functional evaluation versions of our tools

INTELLIGEN, INC. • 2326 Morse Avenue • Scotch Plains, NJ 07076 • USA
Tel: (908) 654-0088 • Fax: (908) 654-3866
Email: info@intelligen.com • Website: www.intelligen.com
Intelligen also has offices in Europe and representatives in countries around the world

This article provides a comparison of the provisions found in ASTM E2500 versus the expectations for equipment qualification as enunciated in the FDA's recent draft process validation guidance.

A Comparison of the FDA's Draft Process Validation Guidance and ASTM E2500

by Robert E. Chew, PE

Introduction

The pharmaceutical/biotechnology industry has shown great interest in the ASTM Standard E2500[1] for the Design, Specification, and Verification of facilities, equipment, and systems. Many companies are attempting to implement this standard. In quite a few instances, organizations responsible for compliance are concerned that this standard represents a significant change from how industry has practiced qualification in the past. There is a further concern regarding terminology (what certain documents need to be called) and the structure of documents with respect to EU regulatory expectations. The FDA's new draft process validation guidance includes expectations for equipment qualification. How do the expectations in this new guidance compare with the approach defined by ASTM E2500, and how can the EU expectations be reconciled with these documents? This article provides an analysis of these provisions and a recommended approach to equipment qualification.

History

ICH Q9, Quality Risk Management, was finalized at Step 4 in November 2005[2] and has been adopted by the Japanese, EU, and US regulators as either guidance or incorporated into regulations. This document provides principles and examples of tools of quality risk management that can be applied to all aspects of pharmaceutical quality, including development, manufacturing, distribution, and the inspection and submission/review processes. One way (out of many) that risk management can be used is to focus the facility and equipment design and operation around risk to the patient. A qualification approach also can make use of quality risk management to focus on those aspects of the facility, equipment, and automation that provide control of risk to the patient, or otherwise help assure manufacture of a quality product.

The EU GMPs Annex 15 on Qualification and Validation, published in 2001, states that "A risk assessment approach should be used to determine the scope and extent of validation." The document then prescribes use of Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) as being precursors to process validation. These terms are defined and general content is specified. These terms and provisions are echoed in the more recent ICH Q7A, GMPs for manufacture of active pharmaceutical ingredients, which has been adopted by the US, EU, and Japanese regulators as either regulation or official guidance.

In July 2007, ASTM E55 committee (which is developing standards related to pharmaceutical manufacturing) issued its Standard E2500 covering the design, specification, verification, and acceptance of facilities, equipment, and associated automation for use in pharmaceutical and biotechnology manufacturing. The purpose of this standard is to describe how to implement the ICH Q9 principles of quality risk management in a controlled and documented manner that meets regulations and demonstrates manufacturing systems are suitable for their intended use.

In November 2008, the FDA issued its draft update to the 1987 Process Validation Guidance. In January, the FDA delivered a webinar on this subject, hosted by ISPE. See related article on page 8 in this issue for a full discussion of the contents of this draft guidance. Industry has been provided with an opportunity to comment

Continued on page 26.

High performance teams make the difference.

COMMISSIONING AGENTS.

Our teams are recognized industry leaders in developing better methods to meet your business and regulatory demands. When schedule is your problem, we are your solution.

Major services include:

- Commissioning planning equipment start-up, troubleshooting, and field execution; verification and qualification (IQ, OQ, PQ)
- Quality Risk Management (QRM) Implementation and Risk Based Qualification Programs
- Validation – Process, Cleaning, Sterilization, Computer
- Process Improvement Services: Process Analytical Technology (PAT), technology transfer, process improvement studies
- Technical services including design reviews, SOP development, training
- Maintenance program development and implementation
- cGMP Compliance Services – audits, regulatory reviews, improvement projects, submission assistance, comparability protocols

CAI
Commissioning Agents, Inc.

Achieve world class manufacturing.

Call Robert E. Chew, P.E., President
Robert.Chew@CAgents.com
+1.317.710.1530

COMMISSIONINGAGENTS.COM

An Employee-Owned Company

on this draft guidance, and it remains to be seen the degree to which comments and changes will be incorporated into the final guidance.

ISPE has under development a new Baseline® Guide Volume 12: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment, which will provide details on how to implement a program based on ASTM E2500. ISPE also is developing a Good Practice Guide that will provide further options and approaches to qualification, including how to evolve practices based on the original Baseline® Guide Volume 5: Commissioning and Qualification, toward an ASTM E2500-based approach.

Terminology

For many years, a *Qualified* system meant that there existed a QA pre-approved, executed, and QA post-approved set of documents consisting of an IQ and OQ (and in many cases a PQ) protocol. For computer systems, and later most systems, this set of documents was expanded to include user requirements, functional requirements, traceability matrices, etc. The content of these protocols more often than not was dictated by local procedures. It did not matter whether the protocol content actually corresponded to critical aspects of the system or whether the qualification process actually yielded equipment that was fully functional and ready to manufacture quality product. What mattered was whether the local procedure was followed to develop, execute, and approve each protocol. Today, there are projects where money is being wasted and time is being lost as decisions are made to address procedural issues that are oblivious to good engineering and science and the impact on product quality.

This is changing. The most important change is what it means to *Qualify* a manufacturing system. This change began with ISPE's Baseline® Guide Volume 5: Commissioning and Qualification. This Guide defined IQ, OQ, and PQ in terms of "aspects…that can affect product quality." This is a more focused approach than the traditional approach of inspecting and testing against all engineering specifications (which can yield very thick protocols, a measure of success for some). ICH Q7A defines DQ as "verification that the proposed design… is suitable for the intended purpose." ASTM E2500 defines verification as "a systematic approach to verify that manufacturing systems…are fit for intended use…" The FDA's new draft Process Validation guidance states, "activities undertaken to demonstrate that utilities and pieces of equipment are suitable for their intended use and perform properly is referred to as *Qualification.*" The draft guidance also states, "Focusing on qualification efforts without understanding the manufacturing process may not lead to adequate assurance of quality." In short, a *Qualified* system no longer means one with signed off protocols created and executed per a rigid procedure, but rather a system that has been shown to be *suitable for its intended use.*

This use of the term *Qualification* to mean a demonstration of suitability for use is equivalent to how ASTM E2500 uses the term *Verification*. The author believes that the term *Verification* has a more narrow and specific meaning in the medical device and other industries: *Verification* is the act of confirming, through objective evidence, that a particular feature or specification has been met. This definition fits with the use of the term verification in ICH Q7A, in that DQ, IQ, OQ, and PQ are defined in terms of "documented verification that…"

The third related term is *Commissioning*. The FDA draft guidance states, "It is essential that activities performed to assure proper facility design and commissioning precede PQ." Commissioning is widely used in many industries, particularly the construction industry; therefore, it is a definition that is readily understood by many parties and is of benefit to project teams.

For purposes of this article, the following terminology will be invoked. For additional discussion of this choice of definitions, please see related article in the July/August 2008 issue of *Pharmaceutical Engineering.*[3]

Verification – the act of confirming, through objective evidence, that a particular specification has been met.

Commissioning – a well-planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations.

Qualification – a state, or determination, that the equipment has been found to be suitable for its intended use.

Basis for Qualification

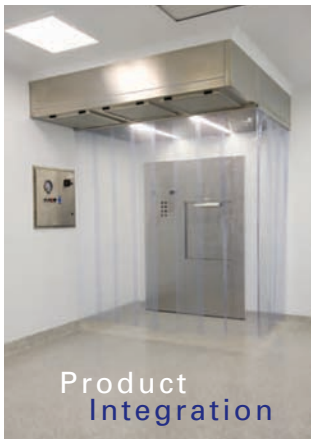
What defines or what constitutes suitability for use? Neither the FDA guidance, nor EU GMPs, address this question in general terms, but instead merely provide examples of qualification activities. See Content and Execution below. ICH Q7A has the general requirement to comply with the approved design and to operate and perform as intended.

The ASTM E2500 standard provides a much clearer definition of what suitability for use is, and how it is assured. While both the FDA draft guidance and the ASTM standard discuss understanding the process science behind manufacturing, the standard goes further to define critical aspects as "functions, features, abilities, and performance characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety." The standard requires the definition of product and process requirements, and the use of risk assessments to identify appropriate controls through design solutions and other means. Collectively, the process requirements and risk assessments can be used to derive the critical design and operating characteristics; these constitute "suitability for use."

The ASTM E2500 standard prescribes a lifecycle approach: "Assurance that manufacturing systems are fit for intended use should not rely solely upon verification after installation, but be achieved by a planned and structured approach applied throughout the system lifecycle." The standard prescribes a series of steps necessary to design, specify, and verify the manufacturing systems. The FDA guidance includes a brief mention of the need to assure proper facility design and commissioning, but does not carry this idea to any greater detail.

Continued on page 28.

A Single Resource...



for TOTAL Cleanroom Confidence.

Planning & executing the right cleanroom solution for your critical process.

AES is your single resource to deliver fast track solutions for Pharma & BIO applications, such as:

- **API Clean Containment**
- **Fill/Finish Processes**
- **Blow/Fill/Seal Facilities**
- **EU/Grade A Laminar Flow Upgrades**
- **Low cost ISO 8/CNC Macro Environments**
- **Cell Manufacturing Facilities**

With the AES Pharma Wall System, combined with our expert knowledge of HVAC and process integration, let us show you how the AES "single resource" team can deliver maximum value to your cleanroom investment.

Call Grant Merrill at 888-237-2532 (ext. 139) to arrange your free consultation today.

aes
Clean Technology, Inc.

1-888-AES-CLEAN ext. 139
237-2532

aesclean.com

The determination, via the ASTM process requirements and risk assessment process, of what constitutes suitability for use is a more robust and process-science driven approach than the FDA guidance "examples." While one cannot argue with the general thrust of these examples, the potential is that industry will focus on these perceived requirements to the detriment of good science and good test engineering practices.

Planning for Qualification

Both the ASTM E2500 standard and the FDA draft guidance are remarkably similar with respect to planning, the only difference being use of *Verification Plan* (ASTM) vs. *Qualification Plan* (FDA). The EU GMPs also contain similar requirements. Table A illustrates the respective requirements for "plans."

Content and Execution

The EU GMPs are the most prescriptive, defining DQ, IQ, OQ, and PQ. Neither the FDA draft guidance nor the ASTM standard defines how the design review and inspection and test programs should be structured; during ISPE's webinar with FDA, the FDA presenter stated that there is no expectation for IQ/OQ/PQ per se. The EU GMPs prescribe content of IQ, OQ, and PQ with IQ having the most prescriptive detail. The FDA draft guidance states, "Qualification of utilities and equipment generally includes the following activities." The examples are similar to the EU content examples and include:

- selection of materials of construction (note the words are selection, not verification!)
- operating principles and performance characteristics appropriate for their specific use
- built and installed per design specifications – and it clarifies this by stating "built as designed with proper materials, capacity, and functions, and properly connected and calibrated."
- Operate in accordance with process requirements in all anticipated operating ranges. This is further amplified to include challenges under load, performance of interventions, start and stoppage as expected during routine operations, and ability to hold operating ranges as long as necessary during routine production operations.

The author feels the above attempts by regulators to engage in the practice of defining the approach and scope of inspections and testing are overly prescriptive. For example, the last sentence regarding the ability to hold operating ranges as long as would be necessary during routine production could lead a team to conclude they have to show the ability to control bioreactor temperature, pH, dissolved oxygen, etc., over a time period equal to a normal cell culture batch, which could be days or weeks. A test engineer would not assess this as being necessary, but would instead understand the science of the process and test those control loops under expected worst case challenge conditions for heat transfer or oxygen uptake, etc. Eventually, of course, such control is by default demonstrated during development batches or process validation lots. However, teams may interpret the guidance regarding qualification of equipment preceding PQ lots as being a hard requirement and endeavor to execute such tests in a non-optimal manner.

The ASTM standard prescribes that specific methods, performance, and documentation of inspection and testing activities are to be determined by subject matter experts. The verification activities should be conducted using a systematic approach and documented, the extent of which is scaled based on risk to patient, risk to product quality, and the complexity and novelty of the equipment. This is a science and risk-based engineering approach. The use of subject matter experts, as defined by the standard, is in complete agreement with 21 CFR 211.25, Personnel Qualifications.

Plan Element	ASTM	FDA	EU
Strategy/studies or tests to use/timing or sequence/scheduling	X	X	X
Define acceptable documentation of detailed activities	X	X	X
QA approval (for systems with critical aspects)	X	X	Note 1
Acceptance criteria	X	X	
Developed and approved by subject matter experts	X		
Responsibilities/organizational structure		X	X
Incorporate risk management to prioritize activities and adjust level of effort in both performance and documentation thereof	X	X	Note 2
Choice to use system-based planning or one overall project plan	X	X	X
Managing change during the project	Note 3	X	X
Validation policy, and reference to existing documents			X
Note 1: Common expectation is that the validation master plan be approved by QA. Note 2: The Principle (preamble) states "A risk assessment approach should be used to determine the scope and extent of validation." It is presumed that the scope and extent are discussed in the validation plan. Note 3: ASTM positions Change Management as a required supporting process to the project, but does not mention it in the context of the verification plan. It is likely teams would choose to include such a subject in their verification plans.			

Table A. Comparison of ASTM, FDA, and EU expectations for contents of a "Qualification Plan (FDA/EU)" or "Verification Plan (ASTM E2500)."

Review, Approval, and Release

ASTM E2500, the EU GMPs, and the FDA draft guidance document all require a summary report following the field inspections and testing. This report is to summarize the findings, highlight any deviations, and describe any changes to the plan/protocol that may have occurred. The ASTM standard describes a two-step process, Verification Review, which is performed by an independent (second check) subject matter expert, followed by an Acceptance and Release, which includes the quality unit for systems with critical aspects. In other words, technical experts review the technical results and make a determination as to suitability for use, while the quality unit provides a final approval of this determination and official release for manufacturing, at which point the system is placed under QA pre-approved change control (vs. change management during the project).

It should be noted that NONE of the three documents describe the typical onerous and formal deviation resolution process present in most projects today. Only the EU GMPs and the ASTM standard mention deviations, and both discuss them in terms of documentation via the final summary report. While the FDA draft guidance does not specifically mention deviations, the subject can be inferred under the contents of the qualification plan: "the criteria appropriate to assess outcomes [should include how to deal with deviations]."

Summary and Recommendations

Table B summarizes the similarities and differences between the US FDA, EU GMPs, and ASTM E2500 with respect to demonstrating manufacturing systems are suitable for their intended use.

It is this author's opinion that if a project team follows the requirements of the ASTM E2500 standard, it will have met the expectations of both US FDA and EU regulators for demonstrating manufacturing system suitability for use. While project teams may choose to be sensitive as to what labels are attached to what documents and to a few particulars of the regulations, overall the ASTM standard provides the most robust, science- and risk-based methodology of any of the documents discussed.

For those who feel more comfortable having documents labeled "DQ, IQ, OQ, and PQ," the following is suggested with respect to documents typically produced during an ASTM E2500-based project.

- The final risk assessment and identification of critical aspects/acceptance criteria and confirmation that the design includes all process requirements could be labeled the DQ.
- A checklist of these critical aspects and their acceptance criteria could be used to review the verification/commissioning work to confirm all critical aspects have been checked.

Concludes on page 30.

Qualification Expectation	ASTM	FDA	EU
Focus on science-based process understanding and meeting process requirements	X	X	
Equipment and facilities suitable for intended use	X	X	
QA approves [qualification] [verification] plan	X	X	
QA approves [qualification] [verification] report	X	X	
QA approves protocols	Note 1	Note 1	Note 2
Risk assessment to "scale" effort, documentation	X	X	X
Flexibility on how effort is structured	X	X	
Specific aspects to check are spelled out		X	X
Critical aspects derived from risk assessments and process requirements	X		
Use of project change management	X	X	X
Use of subject matter experts: how to verify, adjudicate departures from specification	X		
Use of vendor documents	X		
Design and testing of facility, process, equipment based on process understanding	X	X	X
Final report to summarize findings and deviations	X	X	X
Note 1: The QA unit is to approve the acceptance criteria and other high level aspects of the qualification planning effort as discussed under Planning for Qualification. Note 2: QA approval is inferred. EU Annex 15 requires approval of protocols, but does not state by whom.			

Table B. Summary comparison of key expectations of ASTM E2500 program, FDA process validation guidance, and EU GMP Annex 15.

These checklists could be labeled "IQ/OQ" protocols. These checklists could actually be created or copied from the final risk assessment and list of critical aspects, eliminating a separate protocol pre-approval step – the approval of the DQ also could serve as the approval of these checklists.

- A similar approach could be taken for PQ work or a more traditional PQ protocol could be used that includes the specific test cases and instructions for execution.
- These checklists that are labeled IQ/OQ protocols also could be used as the final verification report and the approval thereof would constitute the acceptance and release phase of ASTM standard.

As a cautionary note, it is the author's experience that teams attempting to implement ASTM E2500 with respect to risk assessments and contents of protocols spend significant effort trying to understand and spell out the detailed mechanics of documentation format, structures, what goes where, etc. It also is the author's experience that teams tend to view risk assessments solely through the lens of focusing on the inspection and testing (verification/qualification) effort. That is not the intent of ICH Q9, Quality Risk Management. Instead, it is the author's recommendation that teams approach risk assessments with a holistic view – conduct risk assessments with the idea of identifying, assessing, and controlling risk to the patient through a variety of means (engineering and other quality system-related means). The risk assessments should commence at a high level starting with conceptual design, continuing through more detail as the design develops. It will then become apparent to teams as to how to use these results – to improve the design, to improve procedures, to improve training, to improve other aspects of the quality system, not to mention providing a focus on the critical design and operating aspects of the manufacturing systems.

References

1. ASTM E2500-07: Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment, July 2007.
2. See the FDA/International Conference on Harmonisation (ICH) guidance for industry:
   a. Q8 Pharmaceutical Development
   b. Q9 Quality Risk Management
   c. Q10 Pharmaceutical Quality Systems
3. Adamson, R., Calnan, N., Chew, R., Wisniewski, S., "Commissioning, Qualification, and Verification: A Review Solving the Terminology Conundrum," *Pharmaceutical Engineering*, July/August 2008, Vol. 28 No. 4.

About the Author

Robert E. Chew, PE is President and CEO of Commissioning Agents, Inc. and has 20 years of experience in the pharmaceutical industry. He was a member of the Author Task Team which produced the recent ASTM E2500-07 International Standard. Chew also is a member of the team currently writing the ISPE Baseline Guide Volume 12: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment. He is a former member of ISPE's International Board of Directors, and has been a frequent speaker for ISPE globally. He graduated in 1981 with a BS in chemical engineering from Case Western Reserve University. He can be reached by telephone: +1-317-710-1530 or by email: Robert.Chew@Cagents.com.

Commissioning Agents, Inc. P.O. Box 34320, Indianapolis, Indiana 46234 USA.

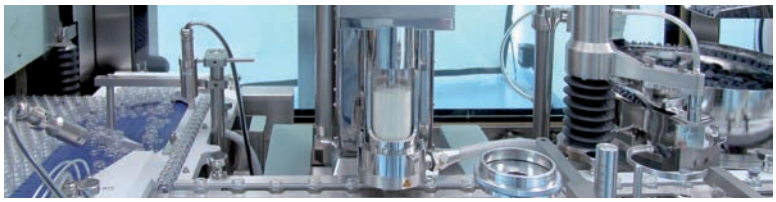
Ad

A compact, clearly structured machine concept for a pharmaceutical company in Austria

Powders today, liquids tomorrow

A multitude of functions for pharmaceutical powders – with the option to fill liquids. And here's the functional process: At first, the glass containers are placed into a washing machine, where they are cleaned and dried. Subsequently, they are hot-air treated in the sterilizing tunnel and later cooled: the cooling zone is sterilizable for this purpose. After the vials are transferred to an interim buffer, they are conveyed to the filling and closing machine in a space-saving solution.

To portion the target weight of 100 mg powder per container with minimum tolerance, the powder dosing requires absolute precision. To achieve such outstanding accuracy, the auger filling system is connected to a 100% in-process-control. An ongoing statistical evaluation of data forms the basis for the tendency control of the doser, so that filling weights are continuously aligned with optimum weight.



Clearly structured design of the line, despite a multitude of functions and lack of space at the customer's site.

Filling is followed by closing – or vacuum drying. Depending on the program pre-selection, either the filling and closing machine places, or inserts plugs within the isolator-protected zone. In the first variant, the containers with the loosely placed plugs are conveyed to an automatic filling and discharge unit feeding the vacuum dryer. The vacuum dryer reduces residual humidity of the filled powder to the defined value.

Following automatic discharge, the vials are closed by a crimping machine processing the bottles independently from height tolerances.

There are no limits to processing liquid sterile pharmaceutical in "parallel" to filling powders, thanks to technology and design. In addition, the vacuum dryer can be upgraded to freeze drying. The concept is transparent and compact, despite its extreme complexity and flexibility – with cameras and sensors, plus a SCADA system additionally ensuring safe machine operation and control.

OPTIMA GROUP

pharma

INOVA
KUGLER
KLEE

OPTIMA GROUP pharma GmbH
Otto-Hahn-Str. 1, 74523 Schwäbisch Hall, Germany
www.optima-group-pharma.com

OPTIMA Machinery Corporation
1330 Contract Drive, Green Bay, WI 54304, USA
www.optima-usa.com

Optima Group is global: In the USA, Mexico, Brazil, France, United Kingdom, Italy, Japan, Korea, China and Germany

Jean-Louis Robert talks candidly about his role with the International Conference on Harmonization (ICH), the continued importance of harmonizing quality standards both within the ICH regions and beyond, and the need for global implementation of initiatives such as Quality by Design (QbD), design space, and risk management.

PHARMACEUTICAL ENGINEERING Interviews

Dr. Jean-Louis Robert, Head of Luxembourg's Laboratoire National de Santé, Service du Contrôle des Medicaments

by Dr. John C. Berridge

The following is a recent interview with Jean-Louis Robert, Head of Luxembourg's Laboratoire National de Santé, Service du Contrôle des Medicaments, conducted by ISPE's European Regulatory Affairs Advisor, who was a European Industry Representative at the International Conference on Harmonisation (ICH) from its inception until 2007.

Dr. Jean-Louis Robert studied chemistry at the University of Basle (CH) and obtained his PhD from there in 1976. He had a post-doctoral training at the Pharmaceutical Institute of the "Eidgenössische Technische Hochschule" (ETH) in Zurich (CH). He spent one year with a pharmaceutical company before joining the National Health Laboratory (LNS) in Luxembourg. In his current position, he is Head of the Department of Control of Medicines, an Official Medicines Control Laboratory (OMCL) at the LNS, member of the European Directorate for the Quality of Medicines OMCL (Council of Europe, Strasbourg) network. He has been a member of the Committee for Human Medicinal Products (CHMP) since 1995 (co-opted since 2004) at the European Medicines Agency (EMEA) in London and Chairman of the CHMP/CVMP Quality Working Party since 1995. Within the International Conference on Harmonization (ICH), he is or was involved in following topics: Validation of Analytical Procedures (Q2), Common Technical Document-Quality, revision of the guidelines on impurities (Q3A and Q3B), Pharmaceutical Development (Q8), Pharmaceutical Quality System (Q10), and currently he is Rapporteur for the implementation of ICH Q8, Q9, Q10. At the European Pharmacopoeia, he is a member of the Commission and of the group of experts 10 B (synthetic products). Currently he chairs the Steering Committee of the Certificate of Suitability of the European Pharmacopoeia. He also serves as a pharmaceutical expert at WHO.

Q Jean-Louis, today you contribute to a wide variety of activities associated with public health protection. For example, you are the quality representative to the EMEA's Committee on Human Medicinal Products (CHMP) and the Chairman of the Quality Working Party (QWP). For many years, you and I worked closely together as members of a variety of ICH Expert Working Groups. Your latest ICH contribution has been the completion of the Annex to ICH Q8 in November 2008. Congratulations! This surely represents the conclusion of another very valuable ICH guideline.

A Yes, thank you. I was very happy to take over the completion of this guideline after you had led the Expert Working Group through to Step 2 in the ICH process. While principles of Quality by Design (QbD) were not totally new in Europe, it is extremely useful to have a guideline such as Q8(R1) to explain an enhanced approach to pharmaceutical development and all the opportunities linked to it.

Q Can you tell me more about your role and responsibilities as Head of the Laboratoire National de Santé, Service du Contrôle des Medicaments in Luxembourg?

A I am responsible for the laboratory which deals primarily in the quality control of the medicines sold in Luxembourg. This monitoring

is done in close collaboration with the Division of Pharmacy and Medicines (Luxembourg Inspectorate) at the national level, and they are responsible for the review and approval of human and veterinary dossiers in Europe. The laboratory is also involved in developing methods to characterize the chemical and physical properties of drugs at pharmacopoeial level. The laboratory is a member of the European Official Medicines Control Laboratories (OMCL) network, coordinated by the European Directorate of Quality of Medicines (Council of Europe, Strasbourg). It is also engaged in anti-counterfeiting activities.

Q Please tell me more about the role and responsibilities of an OMCL.

A An OMCL is an official laboratory that supports the regulatory authorities and complements the inspection services in controlling the quality of medicinal products on the market by independent testing. It is an independent laboratory responsible for the quality control of medicines for human and veterinary use in member states of the Convention on the elaboration of the European Pharmacopoeia and the observer states. The Commission of the European communities and the Council of Europe set up the network in May 1994 and the European Secretariat took on this new responsibility. The main purpose of the European network of OMCLs is the mutual recognition of tests carried out at the national level from countries that belong to the European Union and the sharing of expertise, standardization, and international collaboration for the other countries. Among the many things the network does, it has set up a coordinated European approach for the surveillance of marketed products. It is also responsible for the coordination of the official batch release of vaccines, for example.

Q As an EU expert with the EMEA and representative to the CHMP, what are the main areas that you focus on and contribute to?

A At the CHMP level, my main contributions are for the pharmaceutical quality aspects of submissions. I was nominated to the CPMP, as it was then, in January 1995 and became a co-opted member of the CHMP in 2003. The harmonization of quality standards across Europe is the responsibility of the Quality Working Party (QWP). I have chaired the QWP since March 1995. As an EU expert, I support the activities of the European Directorate for the Quality of Medicines (EDQM) European Pharmacopoeia, OMCL network, and represent Europe in the International Conference on Harmonisation (ICH).

Q Tell us more about the role of the QWP and why is it so important to have an organization such as the QWP?

A As Europe continues to grow, it is vitally important to have a coordinating organization that oversees the development, implementation, and application of common standards and quality systems across all the member states. Where we see the need to develop a guideline for industry regarding a quality matter, we address it through a well-documented and rigorous procedure. We actively seek input from industry and other interested parties across the whole of the community and are always willing to hear comments and suggestions on how we can improve quality standards in Europe, and internationally, for the benefit of patients.

The QWP also represents a single source of scientific advice for industry. We hold regular meetings with companies who seek our input as they progress their candidates through the later stages of development.

In addition, the QWP provides a central point of contact and liaison with other regulatory authorities. For example, we recently collaborated with Health Canada in the elaboration of a guideline for inhaled products, and we frequently welcome visitors from the FDA or other agencies to our QWP meetings. For instance, Swissmedic and the European Pharmacopoeia participate as observers to our meeting.

Q What are your current key priorities as Chairman of the QWP? How do you see the role and priorities of QWP changing or developing over the next decade?

A Right now, our priorities can be seen by reviewing the work programmed on our Web site. In the recent past, we have significantly increased our collaboration with the Inspectors' working party where we are planning greater involvement of assessors with inspectors as we review and approve new marketing authorization applications. We work very closely with the Biological Working Party and this has been especially so with the development of the recent ICH guidelines. Looking further into the future, of course we will continue to adapt to new scientific progress and work across Europe to support the training of assessors, where there may be opportunities to work together with organizations such as ISPE. We do also have a very active PAT team, addressing specific issues with regard to PAT, Quality by Design, giving advice to industry on product related issues. This group chaired by Dr. Keith Pugh from MHRA includes experts from QWP, BWP, and GMDP IWP.

Q Tell us more about your role in ICH. I believe you are the longest serving member of the Quality Expert Working Groups?

A With your recent retirement, I think I am now the longest serving member supporting the quality topics! Clearly, my primary role is to represent the EU in this area. I have really enjoyed working for the past 15 years and still enjoy supporting the harmonization of quality standards both within the ICH regions and those observer countries that adopt the ICH guidelines. One of the more demanding roles is that of the rapport. Generally, industry acts as the rapport until a guideline reaches step two, after which the regulatory authority from the same region will take over the responsibility. Personally, I have led the development of the guidelines concerning analytical validation, impurities (revision), pharmaceutical development part of, the quality aspects of the CTD-Q, and currently Q8, Q9, and Q10 IWG.

Q There are many different initiatives (FDA's initiative on Pharmaceutical Quality Systems for the 21st Century, ICH Guidelines, industry association

Concludes on page 34.

initiatives, etc.) that share the same concepts (some of which are not so "new"), such as QbD, design space, risk management, etc. What do you think is the best way forward to facilitate global implementation of those concepts?

A There are probably two ways which we can facilitate the global implementation of these concepts. Starting with ICH Q8, we have been focusing more on creating a higher level of guidance that is less prescriptive than was perhaps the case with earlier guidelines. This means that there then needs to be agreement on interpretation. Since it is industry, not regulatory authorities, that develops new drugs, it is important for industry to develop and share their understanding on the interpretation and implementation of these guidelines. For example, there have been a number of groups that have developed and published case studies and other training materials that support the implementation of these guidelines. The more we can do that and the more that we can jointly collaborate in their development and elaboration, the greater will be the adoption throughout the world. Secondly, we just need to continue the dialogue. No guideline is ever 100% complete. There will always be questions. The recently established Implementation Working Group (IWG) has a role to document and answer these questions and thereby provide a valuable resource to support the global implementation of the ICH quality guidelines.

Q What is your involvement with ISPE?

A I have enjoyed many years of involvement with ISPE. In addition to contributing to meetings and workshops in both Europe and the USA, I participate in the Regulatory Affairs Committee meetings and contribute to the International Leadership Forum, which is where senior regulators from around the world and Industry executives can share issues relating to quality and make proposals for their resolution.

Q In what ways do you believe a global organization such as ISPE can assist regulators, pharmaceutical companies, and individuals in the international arena, especially in global implementation of these many initiatives?

A I think it is the combination of expertise and the global reach of organizations such as ISPE that facilitates global implementation. ISPE, with its Communities of Practice (COPs), Education Committees, Regional Affiliates, and extensive guides and technology based learning, bridges regulators and industry, and is a powerful resource that can assist everyone whatever region they operate in.

Q In your career, what are the most significant issues or changes you have seen in the global pharmaceutical environment and what changes or challenges do you anticipate in the next few years?

A There have been so many. What I am really pleased to see is the move from assuming quality can be controlled by end product testing to the appreciation of the importance of product and process understanding, thereby supporting continual improvement. The size of the application file has increased though! I've also seen a significant drift away from localized European manufacture to globalized outsourcing, and I do have a concern as to whether industry will be able to maintain their quality standards.

Q For our readers who might want to follow in your distinguished footsteps, what education and preparation is needed for a career in a regulatory agency, particularly as a pharmaceutical assessor?

A Of course there are many routes that one can take to become a pharmaceutical assessor. Studying pharmacy is obviously a good route into regulatory activities, but the scientific degrees of chemistry or biology are also appropriate. These days, I would recommend that a period in industry to gain a wide exposure to contemporary pharmaceutical technology is valuable before considering entering a regulatory agency. I started my career with a BSc in chemistry and then did my PhD in Basle. I stayed in Basle to do a post-Doc at the ETH, and then took my first post in industry at Merck in Darmstadt. I then moved to the laboratory in Luxembourg in 1978 and have been there ever since. The most important is not so much what somebody has studied, but to continuously improve one's scientific knowledge and to be open minded.

Q What has been your most fulfilling role in your career?

A I have really enjoyed working in a small agency because it provided me with a diverse range of opportunities, including the chance to review dossiers (first in the BENELUX registration), to work as part of the OMCL network, and to support the European Pharmacopoeia. I have really enjoyed participating in the development of the EMEA, the establishment of the CPMP/CHMP, and the OMCL network. Of course working in the ICH also has been very exciting. Just for the record, I have not missed a single QWP meeting since it was set up!

Q What kinds of activities do you enjoy in your free time?

A I love being with my family. While I used to play football, jog, and play squash, I spend more time now on my bicycle and I really enjoy the wild and rugged scenery of our local Ardennes. I relax by reading -- thrillers, history, and political commentaries.

Q Are there any other comments/last thoughts you would like to convey to our readers?

A Maybe I can finish this interview with a message to my industry friends and colleagues. I think industry needs to be its greatest critic. It really is important for you to do all you can to achieve the greatest understanding of each other and an understanding of the authorities that regulate you. Do what you can to build trust. We, the authorities, welcome open discussions and transparency, and are always willing to receive new ideas and suggestions from you. As you engage in more and more outsourcing, do pay attention to the quality systems throughout the whole of your supply chain to ensure the robust quality and sustainability of all your supplies.

Filling instinct.

The time has come to take control. IMA Life introduces the latest technological breakthrough in sterile filling: XTREMA F2000. High performances, superb flexibility and easy implementation allow you to bring your sterile processing environment in line with your production objectives, adapting to your needs as they evolve.
Industry experience, proven technology, IMA Life expertise: ingredients which make the XTREMA F2000 much more than a machine.

Come face to face with XTREMA F2000 at Achema 2009
www. ima.it/xtrema

ACHEMA 2009 Frankfurt - May 11-15, 2009/ Hall 3.0 - Stand M2-P21

IMA LIFE S.r.l. • *mktg.filling@ima.it* • *www.ima.it*
IMA NORTH AMERICA, INC. • *sales@imausa.net* • *www.imanorthamerica.com*

IMA LIFE
Aseptic Processing & Filling Solutions

VIAL LOADING • WASHING • DEPYROGENATING • FILLING • FREEZE-DRYING • STOPPERING • CAPPING

PQLI® – What is it?

by Dr. John C. Berridge

This article presents the current status of ISPE's PQLI initiative. It details how PQLI will provide the global industry with the tools necessary to implement the ICH quality vision.

Current Status

ISPE launched its Product Quality Lifecycle Implementation (PQLI®) initiative in June 2007 to help industry find practical approaches to the global implementation of recent ICH guidelines. Through PQLI, ISPE is spearheading approaches to assist in the implementation of, in particular, ICH Q8(R1) (Pharmaceutical Development), Q9 (Quality Risk Management), Q10 (Pharmaceutical Quality System) and imminent Q11, and to support the work of the ICH Implementation Working Group. ISPE is working with industry and regulatory leaders worldwide to support pragmatic and practical implementation of the guidelines based on sound scientific, engineering, and business principles. Key goals of PQLI include the provision of a technical framework comprising, for example, explanatory documents and illustrative examples, supporting the implementation of enhanced science- and risk-based approaches to product realization, technology transfer, commercial manufacture, and its continual improvement in both research- and generic-based organizations. PQLI clearly recognizes that there is no one way to implement the ICH guidelines, rather there are many perfectly satisfactory ways to address the concepts that are described. PQLI is therefore developing a variety of tools to communicate science and risk-based processes, and a growing series of publications demonstrates the areas of current activity (see References).

PQLI encompasses the whole of the product

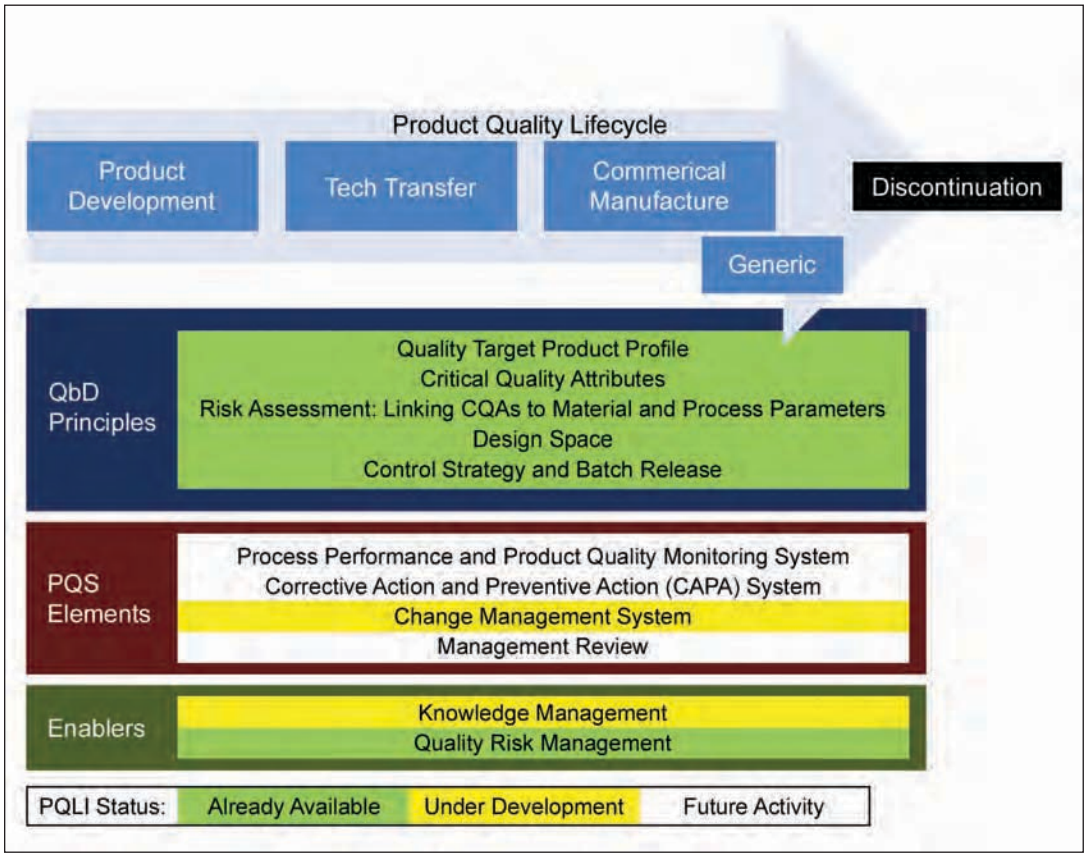


Figure 1. The strategic themes, structure, and status of PQLI.

"Within PQLI, ISPE has established multi-disciplinary, multi-national teams in support of these strategic themes, addressing them from the perspectives of both small molecules (chemically derived) and biotechnology."

lifecycle and comprises three strategic themes - *Figure 1*.

- Principles of Quality by Design
- Pharmaceutical Quality System Elements
- Enablers

These strategic themes represent the key components of the ICH quality vision described at the July 2003 meeting in Brussels which supported the development of the recent ICH quality guidelines:

> *"Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science."*

Within PQLI, ISPE has established multi-disciplinary, multinational teams in support of these strategic themes, addressing them from the perspectives of both small molecules (chemically derived) and biotechnology. Ensuring alignment with the published ICH guidelines and supporting the future IWG activities is a major focus of PQLI. The PQLI teams benefit enormously though the presence of past and current members of ICH Expert and Implementation working groups and they have further benefitted from input and feedback from members of the three ICH regulatory authorities.

Principles of Quality by Design

The principles of Quality by Design (QbD) are described in ICH Q8(R1). Three multinational, multidisciplinary teams were set up to address the priority topics of Criticality (Critical Quality Attributes and Process Parameters), Design Space, and Control Strategy. Through their deliberations a set of papers was published in the Journal of Pharmaceutical Innovation in June 2008. These papers were published with requests for comments, and from the feedback received it is clear there is a continuing need for PQLI to demonstrate how the concepts of the ICH guidelines translate into practical application in all areas of the product lifecycle. Industry continues to ask to see the high level ICH concepts made simple, real, and practical. A more comprehensive explanatory paper is in preparation to show how the different elements of QbD fit together. Case studies and worked examples are a helpful way of exemplifying the principles and the PQLI teams are actively developing such examples. These examples are all aimed at providing clearer options that demonstrate there are many ways of implementing an enhanced, Quality by Design approach rather than suggesting there is just a single way.

The principles of QbD are applicable throughout the lifecycle, and a publication in JPI (March 2009) describes processes and examples which demonstrate this and show how their application can result in significant business benefits. The paper provides three contrasting case studies which indicate a wealth of opportunities to improve processes for existing products through the use of science- and risk-based approaches, and the subsequent business benefits and regulatory opportunities that can accrue.

The principles of QbD also are equally applicable to biotechnology products. PQLI has an international team of industry experts assembling technical guidance and examples to support this sector of our industry.

Pharmaceutical Quality System

As described in ICH Q10, the opportunities to change the paradigm of development and manufacturing activities for full utilisation of enhanced scientific approaches come only with an integrated and robust pharmaceutical quality system. At our planned conferences in 2009 in Washington, Strasbourg, and San Diego, PQLI is organizing presentations and workshops to

Continued on page 38.

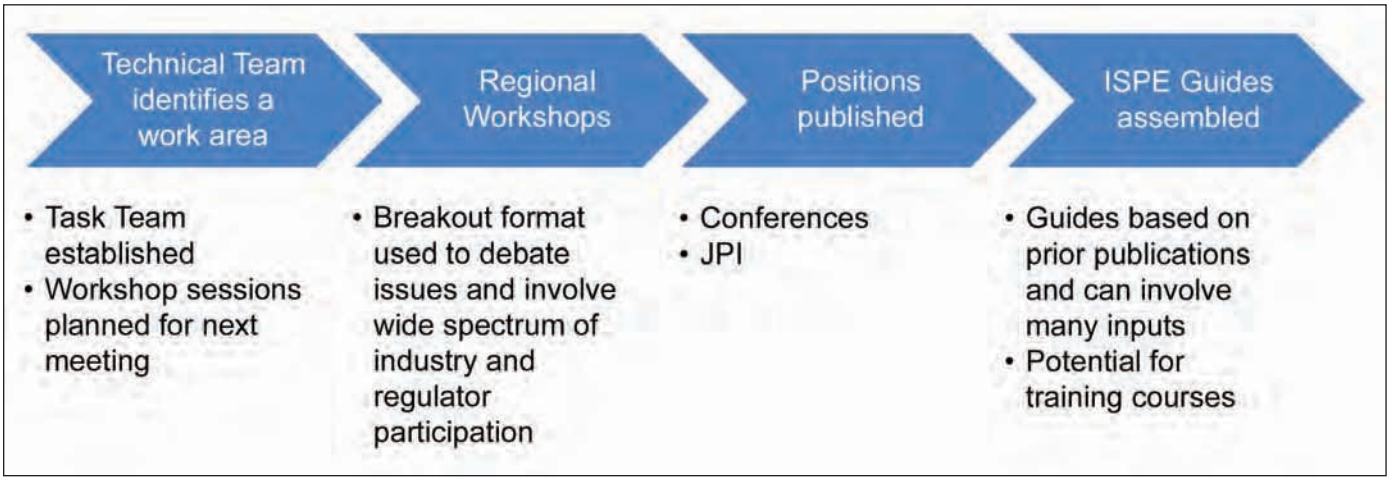


Figure 2. PQLI process to generate technical implementation guidance.

explore the issues and potentially spawn further topic teams to develop the appropriate technical tools.

Enablers

The two enablers described in ICH Q10 are knowledge management and quality risk management. PQLI is addressing quality risk management primarily through the tools being developed to support QbD principles. Knowledge management is a vital enabler that has received little attention so far, but represents the key theme of ISPE's Strasbourg Conference in September 2009 "Managing Knowledge through Science and Risk Assessment."

Future Plans

PQLI will continue its efforts to assist in the adoption and implementation of the ICH quality vision. The goal is to provide a set of resources useful to small, medium, and large innovator companies working on chemical and biotechnology active ingredients and products as well as generic companies. For established concepts, those that are already well-defined by guidelines and the ICH implementation working group, PQLI will continue to support and complement implementation topics with practical case studies, training opportunities and extension of the understanding to global audiences. For example, PQLI has in preparation a technical guide which will describe the continuum of development of a product through to manufacturing and consideration of opportunities for continual improvement. Incorporating the feedback received on the June 2008 JPI papers, it pulls together the foundation work on critical quality attributes and process parameters, design space, and control strategy, linking to many case studies and examples illustrating implementation.

For newer concepts, PQLI will support further debate and discussion through papers, conference presentations, and workshops that involve both industry and regulators: this well established process is illustrated in Figure 2 and is being used to develop implementation guidance around strategic themes 2 and 3.

Conclusions

The vision of the ISPE PQLI initiative is to make available to our global industry the technical and scientific tools and understanding that enable comprehensive implementation of the ICH quality vision. We are fortunate to have on our teams industry experts, current and past members of ICH Expert Working Groups, and to receive excellent feedback from leading regulators across the ICH regions. Building on a foundation of the principles of QbD, PQLI is strengthening this work and now addressing the remaining elements described in ICH Q10 to provide a unique and comprehensive technical framework and set of guides.

ISPE welcomes all contributions, from both members and non-members, who have ideas and examples that describe the practical application of the new ICH quality guidelines. ISPE is keen to collaborate with colleagues and organizations who share the same objectives towards rapid and comprehensive support of the implementation of the ICH quality vision.

If you have any comments, or contributions you wish to make to PQLI, please feel free to email PQLI@ispe.org.

References

PQLI Publications

1. Garcia, T., Cook, G., and Nosal, R., PQLI Key Topics - Criticality, Design Space, and Control Strategy, Journal of Pharmaceutical Innovation (2008) 3:60–68.

2. Nosal, R., and Schultz, T., PQLI Definition of Criticality, Journal of Pharmaceutical Innovation, (2008) 3:69–78.

3. Lepore, J., and Spavins, J., PQLI Design Space, Journal of Pharmaceutical Innovation, (2008) 3:79–87.

4. Davis, B., Lundsberg, L., and Cook, G., PQLI Control Strategy Model and Concepts, Journal of Pharmaceutical Innovation, (2008) 3:95–104.

5. Bolton, R., and Tyler, S., PQLI Engineering Controls and Automation Strategy, Journal of Pharmaceutical Innovation, (2008) 3:88–94.

6. Berridge, J.C., PQLI®: Current Status and Future Plans, Journal of Pharmaceutical Innovation, (2009) 4:1–3.

7. Potter, C., PQLI Application of Science- and Risk-based Approaches (ICH Q8, Q9, and Q10) to Existing Products, Journal of Pharmaceutical Innovation (2009), 4:4–23.

Other Associated or Referring Publications

8. Ende, D., Bronk, K.S., Mustakis, J., O'Connor, G., Santa Maria, C.L., Nosal, R., Watson, T. J. N., API Quality by Design Example from the Torcetrapib Manufacturing Process, Journal of Pharmaceutical Innovation, (2007) 2:71–86.

9. Somma, R., Development Knowledge Can Increase Manufacturing Capability and Facilitate Quality by Design, Journal of Pharmaceutical Innovation, (2007) 2:87–92.

10. Drennen, J.K., III, Editorial: Introducing PQLI Innovations from ISPE's Product Quality Life Cycle Implementation (PQLI) Initiative, Journal of Pharmaceutical Innovation, (2008) 3:59.

11. JPI Interviews Moheb Nasr, PhD, Director, Office of New Drug Quality Assessment (ONDQA), CDER, US FDA, Journal of Pharmaceutical Innovation, (2007) 2:67–70.

About the Author

Dr. John Berridge retired from Pfizer Global Research and Development at Sandwich in January 2006 as Vice President of Pharmaceutical Sciences. He spent more than 31 years at Pfizer, starting as an Analytical Chemist, and more recently responsible for all aspects of chemistry, pharmacy, analytical, and regulatory CMC in Europe. His research interests have been directed toward high performance liquid chromatography with special emphasis on the use of chemometrics. This research was recognized by the award of the Chromatographic Society's Jubilee medal in 1989. Berridge was involved in the ICH processes from their inception until November 2007, representing EFPIA in the Quality topics discussions. He has contributed to guidelines on impurities in drug substances and their dosage forms, specifications, and the Common Technical Document (Quality): he was the Industry rapporteur for the pharmaceutical development guideline (Q8). In 1995, he was presented with an FIP IPS award for his outstanding contribution to industrial pharmacy and in 1997, he was awarded the Royal Pharmaceutical Society Chiroscience award for his services to the pharmaceutical industry. Berridge now acts as an independent consultant and as European Regulatory Affairs Advisor and PQLI project manager to ISPE. He can be contacted by email: pqli@ispe.org.

This article provides a general overview of the organizational structures of the US FDA, EMEA, PIC/S, and ICH as they relate to pharmaceutical manufacturing and regulation. The content in this article is sectioned into three Knowledge Briefs, which are available online and free to ISPE Members.

Global Regulatory Framework Overview: US FDA, EMEA, PIC/S, and ICH

by Dr. Kate McCormick

US FDA

The Food and Drug Administration (FDA) has responsibility for regulation of drugs and biological products which are manufactured and/or sold in the US. The FDA is part of the Health and Human Services Department of the US government. Its role is to guard the welfare of consumers. Full details of the FDA can be found at: www.fda.gov.

The FDA's authority is based upon various laws and statutory documents, as shown in Figure 1. While drugs fall under the Food, Drug, and Cosmetic Act, biological products fall under not only the Food, Drug, and Cosmetic Act, but also the Public Health Service Act.

While the statutes provide the legal basis for the FDA's authority, the regulations which they enforce are contained within the Code of Federal Regulations, Title 21. Of particular importance in relation to manufacturing are parts 210 and 211. These are generally written as 21CFR 210 and 21CFR 211.

Organizational Structure

As Figure 2 shows, the FDA is divided into seven main divisions or Centers. Detailed organization charts can be found at: http://www.fda.gov/oc/orgcharts/orgchart.html.

The Centers and Offices that have particular relevance to the regulation of drugs and biological products are discussed below.

Office of Regulatory Affairs

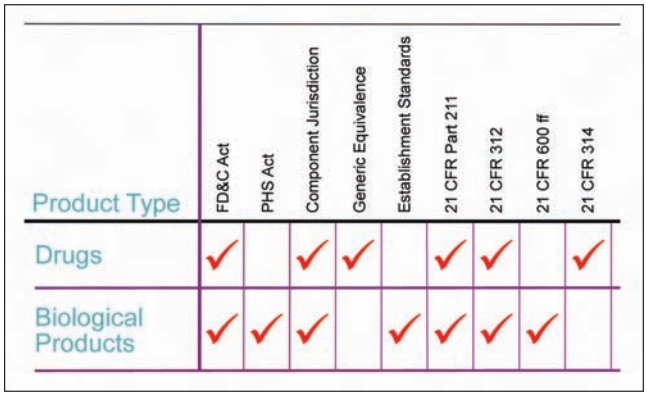
The Office of Regulatory Affairs (ORA) is the lead office for all field activities of the FDA. The duties and functions of ORA are divided between four main Offices: Resource Management, Regional Operations, Criminal Investigations, and Enforcement. ORA regions are the Pacific, Southwest, Central, Southeast, and Northeast regions of the US. Each region supports a number of local FDA offices.

Center for Biologics Evaluation and Research

The mission of the Center for Biologics Evaluation and Research (CBER) is to protect and enhance public health through the regulation of certain therapeutic biological products as well as blood products, vaccines, and tissue and gene therapy products.

Center for Drug Evaluation and Research

The Center for Drug Evaluation and Research (CDER) is responsible for the regulation of chemically-derived and most therapeutic biological products, both new drugs and generics.



Product Type	FD&C Act	PHS Act	Component Jurisdiction	Generic Equivalence	Establishment Standards	21 CFR Part 211	21 CFR 312	21 CFR 600 ff	21 CFR 314
Drugs	✓		✓	✓		✓	✓		✓
Biological Products	✓	✓	✓		✓	✓	✓	✓	

Figure 1. Statutory and Regulatory Authorities.

Center for Devices and Radiological Health

The Center for Devices and Radiological Health (CDRH) is responsible for the regulation of medical devices and radiation emitting products.

Office of Combination Products

The Office of Combination Products (OCP) is an office within the FDA's Office of the Commissioner, which is

Continued on page 42.

Innovation
makes it possible

Telstar Life Science solutions is constantly innovating to offer tailor-made solutions in high technology equipment for the pharmaceutical, biotech and related industries.

With over 45 years of experience and an international presence in more than 100 countries, Telstar is your partner to provide solutions in the following technologies:

Telstar ACE

High Containment Isolators

Telstar Celester

Sterilization Systems, WFI & Pharmaceutical Steam Generation Systems

Telstar Lyo

Freeze Drying Systems

Containment Systems
- Isolators
- Restricted Access Barrier Systems (RABS)
- Downflow booths

Sterilization Systems
- Moist heat sterilization autoclaves
- Chemical agent sterilization autoclaves
- Sterilization and depyrogenation ovens

WFI & Pharmaceutical Steam Generation Systems
- Multiple/simple effects stills
- Pure steam generators

Freeze Drying Systems
- GMP production freeze dryers
- Laboratory freeze dryers
- Loading & unloading systems
- Lyophilization supports services

Laminar Air Flow Systems
- Laminar flow benches
- Biosafety cabinets
- Laminar flow booths
- Customized cabinets

Drying Systems
- Hot air drying
- Vacuum drying

Telstar®
Life Science solutions

TELSTAR LIFE SCIENCES
Josep Tapioles 120
08226 Terrassa (Spain)
T. +34 937 361 600
F. +34 937 859 342
sales.pharma@telstar.eu

TELSTAR NORTH AMERICA
1504 Grundy's Lane,
Bristol, PA 19007 (USA)
T. +1 215 826 0770
F. +1 215 826 0222
telstar.na@telstar.eu

www.telstar-lifesciences.com

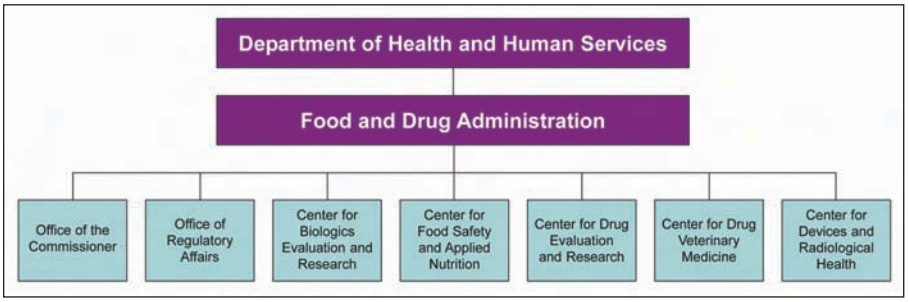


Figure 2. Organizational structure of the FDA.

responsible for general oversight of the agency's regulation of combination products. The primary responsibilities for regulating specific combination products remain in one of the product centers – CDER, CBER, or the CDRH. The OCP is responsible for assigning an FDA center to have primary jurisdiction (lead center) over a particular combination product. The OCP also oversees multi-center reviews of combination products, ensures consistent and appropriate post-approval regulation of combination products, and resolves disputes relating to combination products.

Team Biologics

The FDA Team Biologics was established in 1997 to assure the quality and safety of biological products. It consists of a core team of certified ORA investigators, CBER certified inspectors, and specially trained compliance officers representing both ORA and CBER.

Pharmaceutical Inspectorate

FDA's Pharmaceutical Inspectorate was established under the agency's Pharmaceutical CGMP's for the 21st Century: A Risk-Based Approach. This is a group of certified FDA drug investigators who have received advanced training in drug development, manufacturing, quality assurance, and risk management. These investigators, as well as other FDA drug investigators, inspect all facilities that are regulated by CDER, including those manufacturing therapeutic biological products. The Pharmaceutical Inspectorate is often assigned to inspect the higher risk drug manufacturing facilities.

Licensing/Approval Procedure

Figure 3 shows the approval or licensing process for a New Chemical Entity (NCE) by the FDA. The process, which can take up to 15 years in total, may be divided into 8 phases. Firstly, there is the pre-clinical stage, lasting between 3.5 and 6.5 years. During this stage in-vitro and in-vivo (animal) studies are carried out to assess safety and biological activity. At the conclusion of this stage, the company files an Investigational New Drug (IND) application. In effect, this is a request for a permit for the drug to be transported across state boundaries for the purposes of clinical trials.

Clinical trials are carried out on humans. In Phase I, which lasts up to 1.5 years, the drug is tested on healthy volunteers to prove it is safe and to identify the appropriate dosage.

	Preclinical		Phase I	Phase II	Phase III		FDA		Phase IV
Years	3.5 - 6.5		1 - 1.5	2	3 - 3.5		1.5 - 2.5	15 Total	
Test Population	Laboratory and Animal Studies	File IND with FDA	20 - 80 Healthy Volunteers	100 - 300 Patient Volunteers	1,000 - 3,000 Patient Volunteers	File NDA with FDA			
Purpose	Assess Safety and Biological Activity		Determine Safety and Dosage	Evaluate Effectiveness, Look for Side Effects	Confirm Effectiveness, Monitor Adverse Reactions for Long Term		Review Process/ Approval		Additional Post-Marketing Testing
Success Rate	5,000 Compounds Evaluated			5 enter Clinical Trials			1 Approved		

Figure 3. The FDA approval or licensing process for a New Chemical Entity (NCE).

In Phase II, which lasts 2 years, a small number of patients are voluntarily given the drug to determine its effectiveness and to highlight any side effects.

In Phase III, a much larger population of patients is given the drug to confirm its effectiveness and to identify any adverse reactions over a longer period of time. This phase lasts for between 3 and 3.5 years. Once these phases have been completed, the company files a New Drug Application (NDA) or a Biological Licensing Application (BLA) with the FDA. The process of assessment and approval by the FDA takes between 1.5 and 2.5 years. Once the drug has been approved and is marketed, there is a much larger potential population for further testing. Additional post approval testing related to a drug's approved indication(s) intended to optimize the safe and effective use of the drug is called Phase IV testing.

It can be seen from the bottom of the figure that each approved drug arises from the evaluation of an average of 5,000 compounds.

Pharmaceuticals in the 21st Century

In August 2002, the FDA launched its initiative "Pharmaceutical cGMPs for the 21st Century – A Risk-based Approach." The launch document included the following statement:

"FDA resources will be used most effectively and efficiently to address the most significant health risks."

In other words, the agency does not have sufficient resources to regularly inspect all the sites around the world that are making drugs and biological products for the US market. Hence, it would use risk management to decide the priorities for inspection.

At the same time, it said it required from companies:

"The most up-to-date concepts of risk management and quality systems approaches to be incorporated, while continuing to ensure product quality."

The FDA wants companies to enhance the scientific approach to GMP to emphasize risk-based control point analysis and decision-making. In other

words, for each situation, risks should be assessed as a precursor to deciding what action, and at what level, is appropriate.

While this initiative was launched by the FDA, it is in line with the philosophy of both the EU and Japanese regulators. It is the basis of recent activities within ICH, culminating in the publication of three new guidelines: ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System).

EMEA

The European Medicines Agency (EMEA) (http://www.emea.europa.eu/) has overall responsibility for regulation of medicinal products within the European Union (EU) (http://europa.eu/).

The EU is an expanding group of countries in Europe that have committed to economic and political union. As of 1 January 2009, there are 27 Member States. The current members are shown in Figure 4.

Regulatory Documentation

In terms of regulation of manufacture of medicinal products, all member States are bound by a single set of legislation (Directives) and regulations. In the EU, regulation of medicinal products is the same both for human and veterinary products. However, the legislation is covered by two Directives, both originating from 2001: 2001/83/EC relates to products for human use and, 2001/82/EC relates to veterinary products.

Over time, these Directives have been amended; most recently, they have been expanded to include the manufacture of herbal medicines:

- Directive 2004/27/EC (amending Directive 2001/83/EC on human medicines).
- Directive 2004/28/EC (amending Directive 2001/82/EC on veterinary medicines).

The Directives are expanded and explained via a series of guidance documents.

All these references are contained in "The rules governing medicinal products in the European Community." They are available at: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm.

There are currently 10 volumes covering different aspects of medicinal products from development and registration through to marketing. Volumes 1 and 5 contain all the legislation, including the directives mentioned previously. The remaining volumes contain the guidance documents.

Volume 4 is of specific interest as it concerns good manufacturing practices for medicines. It is divided into two parts: Part I covers the requirements for the manufacture of finished products or secondary manufacturing, as it is sometimes called, and Part II covers the requirements for the manufacture of active substances, also known as Active Pharmaceutical Ingredients (APIs) or sometimes as drug substances.

In addition to Parts I and II, there are a number of annexes. In some cases,

Continued on page 44.

Figure 4. Member states of the European Union (EU) as of 1 January 2009.

these represent the requirements relating to specific types of products, whereas others expand on the requirements of Part I or deal with new concepts that have developed since the main text was published.

The European Medicines Agency

The EMEA was set up in 1995 as the European Agency for the Evaluation of Medicinal Products. It later became known as the European Medicines Evaluation Agency (hence the acronym EMEA), but has since changed its name to the European Medicines Agency.

The EMEA is responsible for evaluation of the safety, efficacy, and quality of products which are submitted for a marketing authorization within the EU. The EMEA:

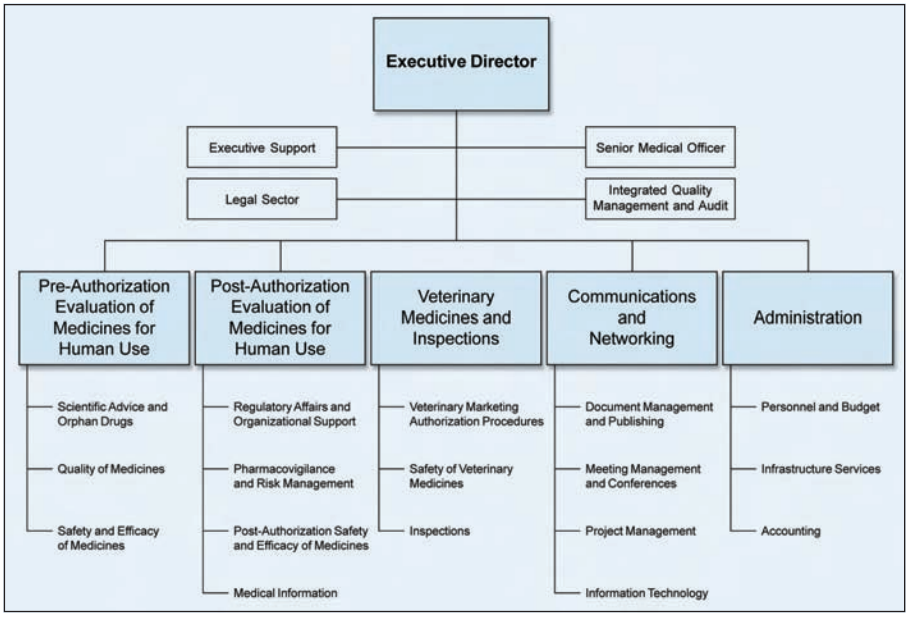


Figure 5. Organizational structure of the EMEA.

- provides independent, science-based recommendations on the quality, safety, and efficacy of medicines and on more general issues relevant to public and animal health that involve medicines.
- applies efficient and transparent evaluation procedures to help bring new medicines to the market by means of a single, EU-wide marketing authorization granted by the European Commission.
- implements measures for continuously supervising the quality, safety, and efficacy of authorized medicines to ensure that their benefits outweigh their risks.
- provides scientific advice and incentives to stimulate the development and improve the availability of innovative new medicines.
- recommends safe limits for residues of veterinary medicines used in food-producing animals for the establishment of maximum residue limits by the European Commission.
- involves representatives of patients, healthcare professionals, and other stakeholders in its work, to facilitate dialogue on issues of common interest.
- publishes impartial and comprehensive information about medicines and their use.
- develops best practice for medicines evaluation and supervision in Europe, and contributes alongside Member States and the European Commission to the harmonization of regulatory standards at the international level.

The EMEA is a scientific body that advises individual Member States and other bodies within the EU and uses a network of scientists from across the EU to facilitate the operation of the evaluation system. It has responsibility for the procedures to authorize pharmaceuticals, monitor them once in the marketplace and withdraw that authorization if there is evidence of a problem. The EMEA also operates information sources and electronic communication in order to enhance the safe use of pharmaceuticals within the EU.

Organizational Structure

The EMEA is located in London. Its organizational structure is shown in Figure 5.

The EMEA is divided into five divisions, three of which involve review and approval responsibilities. One division focuses on pre-authorization (assessment of drugs before they are launched on the market place) while another deals with post-authorization of medicines for human use (evaluation of drugs after they have been launched, primarily through the pharmacovigilance system).

The EMEA inspection section is in the same division as veterinary medicines. However, this is for organizational reasons only; the inspections section relates both to human and veterinary medicines. Communications and administration functions round out the remaining two divisions.

It is important to note that while the EMEA coordinates GMP inspection activities across the Member States, it does not have any inspectors in the section. Each Member State has one or more national inspection bodies responsible for carrying out the inspections. There is mutual recognition of these inspections across all Member States.

Authorization Procedures within the EU

There are a number of different ways in which drugs can be authorized for sale in the EU, depending on the nature of the drug and its supply chain:

Centralized Procedure

For some specific drug types, including biotechnology products, orphan drugs, and veterinary growth enhancers, it is mandatory to use the centralized procedure. A single application is made to the EMEA and authorization, if granted, applies across all Member States.

Mutual Recognition Procedure

For the majority of conventional drugs, the mutual recognition procedure is applicable. As the name suggests, an authorization which has already been granted by one Member State will be recognized by other Member States. In this case, a separate application is required, but a full assessment will not be carried out.

Decentralized Procedure

Under the decentralized procedure, which also is applicable for conventional drugs, an application is made simultaneously to a number of Member States. One State is appointed as the Reference Member State to carry out the assessment. Authorization, if granted, will apply within the States to which the application was made.

National Authorizations

It also is possible for a drug to be registered for sale in a single Member State only. This is particularly used for legacy products that are imported from third countries (countries outside of the EU), where the license was in place before the importing countries had access to the EU.

Continued on page 46.

Summary

The role of regulatory authorities like the European Medicines Agency in the scientific evaluation and oversight of medicines is critical in the assurance of both public and animal health. To learn more about the agency and its operations and purview, please visit their web site: http://www.emea.europa.eu/.

PIC/S and ICH

The evaluation and approval of medicines for human use along with responsibilities for inspection and oversight of the manufacturing and distribution of these medicines occurs at numerous agencies around the globe. Manufacturers of pharmaceutical products face substantial challenges in assuring that their products and processes conform to the varied requirements of these agencies. These organizations are the Pharmaceutical Inspection Co-operation Scheme (PIC/S), which is primarily involved in mutual recognition of GMP inspection results between the regulatory authorities of its members, and the International Conference on Harmonisation (ICH), which is primarily involved in harmonized drug regulatory requirements between Europe, the US, and Japan.

Establishment and Purpose of PIC/S

PIC was set up in 1970 under the auspices of the European Free Trade Association (EFTA). Its full title was "The Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products."

PIC is a legally binding treaty between countries. However, under EU law, it is not permissible for individual Member States to sign treaties with countries outside the EU. Only the European Commission can sign such treaties. However, the European Commission is not a member of PIC. If the work of PIC was not to be lost, a compromise needed to be found.

The PIC Scheme (PIC/S) was set up in 1995. It differs from PIC in that it is an informal agreement between regulatory authorities in Member States and is not legally binding. However, its goals are an extension of those of PIC. The purpose of the PIC scheme is:

- to pursue and strengthen the co-operation established between the participating authorities in the field of inspection and related areas with a view to maintaining their mutual confidence and promoting quality assurance of inspections
- to provide the framework for all necessary exchange of information and experience
- to coordinate mutual training for inspectors and other technical experts in related fields
- to continue common efforts toward the improvement and harmonization of technical standards and procedures regarding the inspection of the manufacture of medicinal products and the testing of medicinal products official control laboratories
- to continue common efforts for the development, harmonization, and maintenance of Good Manufacturing Practice (GMP)
- to extend the cooperation to other competent authorities having the national arrangements necessary to apply equivalent standards and procedures with a view to contributing to global harmonization

The PIC/S Web site, www.picscheme.org, is a very useful reference site.

PIC/S Publications

The documentation that is developed and published by PIC/S is useful both for the inspectorates (for whom the references are primarily intended) and also for industry (who can use the references to understand what inspectors are going to look for).

The GMP guide PE009-7 was issued in its latest form in May 2007. It is virtually identical to the EU Part I document apart from minor changes in terminology and one annex.

Other key guidelines include those relating to blood establishments and APIs. The guideline on Site Master Files includes a template that many companies use to write their own SMF.

These and other publications are available in downloadable PDF formats from the PIC/S web site.

Membership of PIC/S

In order to become a member of PIC/S, the authority in question has to demonstrate that it has the organizational framework and procedures in place to apply a GMP inspection system that is at least on a par with those of the other members. This will include a formal quality management system similar to ISO 9000, although it does not need to be externally accredited. The authority also has to demonstrate that it has trained, competent inspectors who can operate the system effectively.

As part of the accession process (and on an ongoing basis) inspectors take part in multinational inspection teams which provides peer review on their systems and practices.

There are currently 37 regulatory authorities, from 34 countries, that are full members of PIC/S, as shown below. (e.g., the Czech Republic and France have 2 authorities, one dealing with human medicines and the other with veterinary products.) Twenty-two of the 27 member States of the EU are included in this number.

At any time, there also will be other regulatory authorities being assessed for membership or having expressed an interest in the workings of PIC/S.

Although all members of PIC/S have to operate to an equivalent standard,

PIC/S Full Members

Argentina, Australia, Austria, Belgium, Canada, Cyprus, Czech Republic (x2), Denmark, Estonia, Finland, France (x2), Germany (x2), Greece, Hungary, Iceland, Ireland, Israel, Italy, Latvia, Liechtenstein, Malaysia, Malta, Netherlands, Norway, Poland, Portugal, Romania, Singapore, Slovak Republic, South Africa, Spain, Sweden, Switzerland, United Kingdom

PIC/S Partners

European Directorate for the Quality of Medicines and Healthcare (EDQM), European Medicines Agency (EMEA) and UNICEF.

Concludes on page 48.

Pharmaceutical Processing Systems

GEA Pharma Systems supplies the world's pharmaceutical companies with state-of-the-art solutions for the processing of active pharmaceuticals, ranging from the processing of API (Active Pharmaceutical Ingredient) to the production of solid dosage forms and sterile liquids finishing.

The GEA Pharma Systems portfolio of leading industry brands includes:

- Aeromatic– Fielder and Collette granulation/drying systems
- Buck contained materials handling systems
- Courtoy advanced tablet presses
- Niro spray drying technology
- Lyophil freeze drying systems including automatic loading and unloading

The combination of these strong brands with a deep commitment to research and development has resulted in GEA Pharma Systems establishing a leading global market position.

Engineering Excellence.

GEA Pharma Systems

9165 Rumsey Road • Columbia, MD 21045
Tel 410 997 7010 • Fax 410 997 5021
E-mail info@niroinc.com • Website www.niroinc.com

they are not all using the same reference documents. For example, the 22 members that also are Member States of the EU will be using Volume 4 Parts I and II.

Other members, such as Canada and Australia, will have their own national documentation. However, if these documents were examined in detail, it would be very difficult to identify significant differences in the principles being expressed.

Establishment and Purpose of ICH

The full title of ICH is "The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use." ICH was set up in 1990 as a joint forum between regulatory authorities and the pharmaceutical industry, with a focus on harmonizing the procedures used to evaluate the safety, quality, and efficacy of medicines. At that time, companies were experiencing difficulties in submitting dossiers for product licenses in different countries and regions due to differing regulatory expectations.

The purpose of ICH was to identify ways in which greater harmonization could be achieved in the interpretation and application of technical guidelines and requirements for product registration. This would reduce the need for duplicate testing during research and development of new medicines.

The objective was therefore more economical use of resources, and elimination of unnecessary delay in the development and availability of new medicines while maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

Since the emphasis was on products containing new drugs, the scope of the activities was limited to registrations in Western Europe, Japan, and the US, where the majority of new medicines are currently developed.

Work occurs within ICH by means of Expert Working Groups which are appointed to develop guidance on specific topics. In the past few years, the scope of ICH discussions has widened to include not only R&D, but also activities relating to manufacturing.

The ICH Web site can be found at: www.ich.org.

ICH Publications

Unlike PIC/S, publications from ICH are for direct use in industry. Topics are subdivided into four categories:

- Quality topics, relating to chemical and biotechnical active ingredients and to pharmaceutical products
- Safety topics, relating to in vitro and in vivo pre-clinical studies
- Efficacy topics, relating to clinical studies in human subjects
- Multidisciplinary topics, where experts from more than one discipline collaborate in the development of guidelines which do not uniquely fit into one of the above categories

In the first category, Quality topics, a widening of scope has been seen. For example, it was via ICH that the guideline for Active Pharmaceutical Ingredient (API) manufacturing has been formalized, with the publication of ICH Q7 Good Manufacturing Practices for Pharmaceutical Ingredients. This has since been incorporated into the regulatory guidance of the EU, Japan, and the US. More recently, a new ICH Quality Vision was developed which spawned guidelines in support of a greater emphasis on science and risk-based approaches.

Three key documents have been produced to date:

- ICH Q8 (R1) Pharmaceutical Development
- ICH Q9 Quality Risk Management
- ICH Q10 Pharmaceutical Quality System

These publications have been the catalysts in creating a major transformation in the ways in which the industry will be developing, manufacturing, and overseeing the quality of future medicines and related products.

For Further Information

For more detailed and related information, the following ISPE resources are available:

1. Overview of FDA – http://www.ispe.org/cs/explore_by_topic/fda_resources
2. What's New at the FDA – http://www.ispe.org/cs/resourcecenter
3. Recent FDA Slide Presentations – http://www.ispe.org/cs/fda_section/recent_fda_slide_presentations
4. What's New at the EMEA – http://www.ispe.org/cs/resourcecenter
5. Knowledge Briefs: http://www.ispe.org/cs/resource_library_section/knowledge_briefs
   - "Quality by Design," by John Berridge, KB-0001-Jun08.
   - "Risk-Based Approaches to Cross Contamination," by Stephanie Wilkins, KB-0004-Oct08.
6. Product Quality Lifecycle Implementation: http://www.ispe.org/pqli

About the Author

Dr. Kate McCormick of Heathside Information Services Ltd, United Kingdom, is a manufacturing consultant with extensive strategic and operational management experience in the pharmaceutical industry, both in the UK and internationally. She has 10 years of line management and 20 years of internal and external consulting experience. She has worked with multinationals, SMEs, non-governmental organizations and national regulatory authorities in more than 50 countries. She is the author of Quality (a textbook within the Butterworth Heinneman pharmaceutical engineering series) and Manufacturing in the Global Pharmaceuticals Industry, the editor of gmp Review and a regular speaker at international conferences. McCormick gained a degree in biochemistry and a doctorate in microbiology, both at London University. She also has a Masters in Business Administration. She is registered as a senior GMP expert within the EU and is eligible as a QP under the terms of the EU directive. She is currently European Education Advisor for ISPE. She can be contacted by telephone: 44-1626-854611 or by email: kate@heathside.com.

This article presents the final data from a survey conducted on the use of barrier isolators for automated fill/finish operations.

Barrier Isolation History and Trends – 2008 Final Data

by Jack Lysfjord and Michael Porter

As the journey in time of barrier isolation technology went from prototypes in the late 1980s and early 1990s to today, there have been questions regarding the need for benchmarking the usage of barrier isolator technology. Another way to say it is; what is everyone else doing in regard to this technology? This survey presents its history and trends. We have attempted to gather as much information as possible to use as a database; however, we also know that we never achieve perfection with all data. Numbers are as good as the data we get, and they are not absolute. Trends are real and that is what should be used for comparison.

This is the sixth survey on the use of Barrier Isolators for automated fill/finish operations that began in 1998. The surveys have been done only on the even years because of the energy content it requires by both the authors and the users. Manual operations in a glovebox are not considered. It is evident that usage of barrier isolator technology continues to become much more common in the industry.

In the advanced aseptic processing arena a new relative has evolved called a Restricted Access Barrier System (RABS). Surveys for this technology were done in 2005 and 2007 with the 2007 data to be presented in another article to be published.

Table A shows 391 total isolators worldwide for aseptic fill/finish applications (that we know of) in 2008 as well as the progression of number of units since 1998. Tables B to D show the major pharmaceutical region breakouts for Asia, Europe, and North America. Figure 1 shows the global deliveries by year. Figures 2 to 4 again show deliveries by year for the three regions.

Some companies embrace technology while others wait. Figure 5 shows companies who have most aggressively embraced the use of isolators. Figures 6 to 8 show the regional breakout information. Table E displays the increasing number of pharmaceutical companies using isolators (99).

1998	2000	2002	2004	2006	2008
84	172	199	256	304	391

Table A. Filling barrier isolators (worldwide).

1998	2000	2002	2004	2006	2008
11	19	30	42	50	59

Table B. Filling barrier isolators (Asia only).

1998	2000	2002	2004	2006	2008
57	85	97	116	146	196

Table C. Filling barrier isolators (Europe only).

1998	2000	2002	2004	2006	2008
35	49	66	90	105	133

Table D. Filling barrier isolators (North America only).

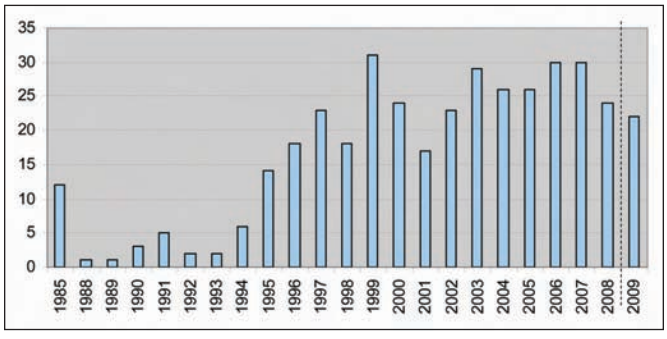


Figure 1. Barrier isolator filling lines – deliveries by year.

ISPE Presents: Technical Documents for the Pharmaceutical Manufacturing and Biotechnology Industries

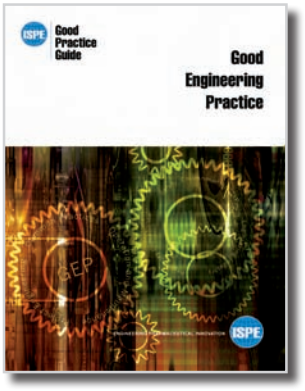
ISPE Good Practice Guide: Maintenance

Item # IGPGMAINT
Member: $145 / €105
Nonmember: $215 / €155

- Published May 2009

The *ISPE Good Practice Guide: Maintenance* provides practical solutions and tools for ensuring quality and compliance of maintenance operations in a regulated industry. Covering current and established practices, this guide helps achieve technical and regulatory accuracy and cost-effective compliance in a new or an existing maintenance program for effective strategy and efficiency. Offering maximum flexibility, this guide clearly helps define roles and responsibilities across cross-functional areas and recommends a systematic approach aimed at continuous improvement of maintenance operations.

The Guide is focused on maintenance in cGMP areas and provides a practical and consistent interpretation of the necessary elements of a pharmaceutical maintenance program. The Guide seeks to enable widespread adaptation and encourage innovation.



ISPE Good Practice Guide: Good Engineering Practice

Item # IGPGGEP
Member: $145 / €105
Nonmember: $215 / €155

- Published December 2008

This first edition of the ISPE Good Practice Guide: Good Engineering Practice covers the complete lifecycle of engineering from concept to retirement.

The Guide:

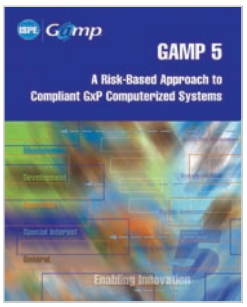
- aims to promote a common understanding of the concept and principles of GEP
- defines and explains the term “Good Engineering Practice”
- describes the fundamental elements existing in pharmaceutical and related industries
- identifies practices, demonstrating how GEP concepts may be applied in the pharmaceutical industry considering the entire range of pharmaceutical engineering activity
- identifies key attributes of GEP, including how GEP relates and interfaces with GxP

ISPE www.ISPE.org/publications

Bookmark: tear along the lines

www.ISPE.org/publications

ISPE Presents: Technical Documents for the Pharmaceutical Manufacturing and Biotechnology Industries

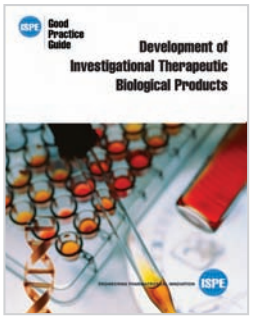


GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems

Item # 5BOUNDUS/ 5BOUNDEU
Member Price: $250 / €185
Nonmember Price: $450 / €375

- Published February 2008

Provides pragmatic and practical industry guidance to achieve compliant computerized systems fit for intended use in an efficient and effective manner. Describes a flexible risk-based approach to compliant GxP regulated computerized systems, based on scalable specification and verification. Points to the future of computer systems compliance by centering on principles behind major industry developments such as PQLI; ICH Q8, Q9, Q10; and ASTM E2500.



ISPE Good Practice Guide: Development of Investigational Therapeutic Biological Products

Item # IGPGBIOL
Member Price: $145 / €105
Nonmember Price: $215 / €155

- Published August 2007

Provides readers with an understanding of issues surrounding product and process development, manufacturing, investigational product supply chain management, quality control/quality assurance, and global regulatory requirements for biopharmaceuticals.

ISPE Baseline® Guide: Active Pharmaceutical Ingredients, a Revision of Bulk Pharmaceutical Chemicals

Item # API0607
Member Price: $200 / €145
Nonmember Price: $400 / €335

- Published June 2007

The first revision in the Baseline Guide series incorporates new regulations and guidance, such as: ICH Q7, ICH Q9, GAMP® 4, 21 CFR Part 11, Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (cGMP), FDA Draft Guidance for Industry PAT – Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance, and much more.

Bookmark: tear along the lines

Save 20% on these great titles and more!

- *ISPE Good Practice Guide: Maintenance*
- *ISPE Good Practice Guide: Good Engineering Practice*
- *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems*
- *ISPE Good Practice Guide: Development of Investigational Therapeutic Biological Products*
- *GAMP Good Practice Guide: Electronic Data Archiving*
- *ISPE Baseline® Guide: Active Pharmaceutical Ingredients, a Revision of Bulk Pharmaceutical Chemicals*

Offer valid at the ISPE 2009 Washington Seminars and Courses,1-4 June 2009. Discount applies to ISPE Members only.

ENGINEERING PHARMACEUTICAL INNOVATION

Container type is shown in Figures 9 to 12. It is interesting to see how, for example, the usage of ampoules and syringes in Asia and in Europe compare to in North America.

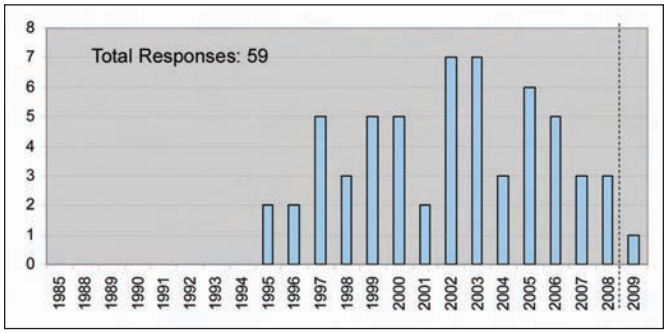


Figure 2. Barrier isolator filling lines – deliveries by year (Asia only).

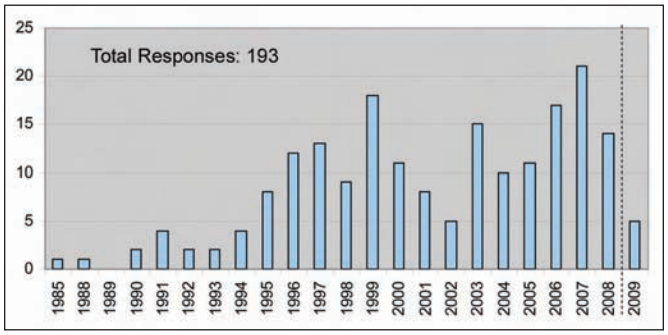


Figure 3. Barrier isolator filling lines – deliveries by year (Europe only).

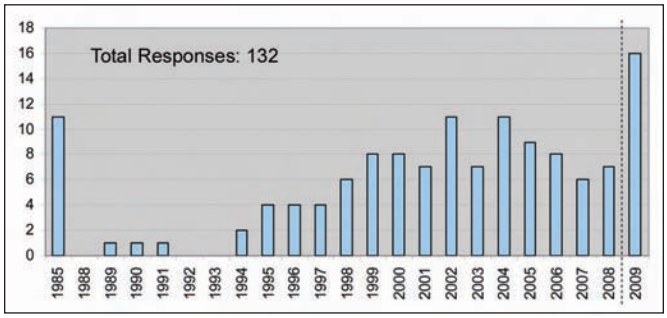


Figure 4. Barrier isolator filling lines – deliveries by year (North America only).

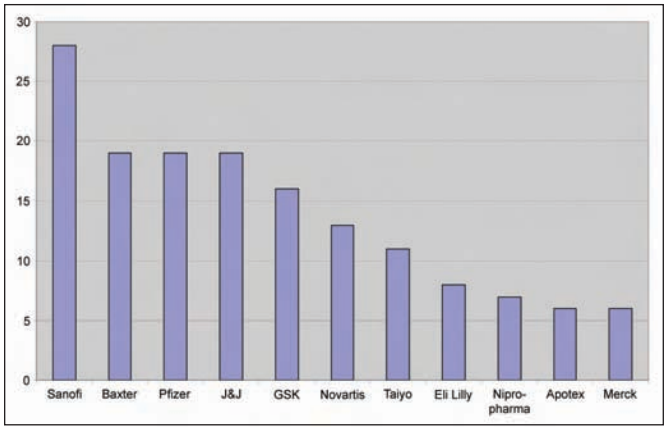


Figure 5. Barrier isolator filling lines – companies with highest usage.

Continued on page 52.

Maximum line speed is shown in the next four graphs 13 to 16. It is interesting to note the majority of isolator usage in North America is for slow speed operation 1 to 100/minute.

Since 1998, the isolators have been hard wall (stainless steel and glass). Soft wall applications were used when the technology started, but reliability, pressure change issues, sterilant absorption, and outgassing pushed the manufacturing to hard wall design.

Surrounding room classification is predominately (65%) ISO 8 in operation with hydrogen peroxide vapor used in 87% of the reported applications for the biodecontamination agent.

Gloves can be one of the most scrutinized areas by regulators. Type of glove used is a decision to be made by users of the technology. Two piece gloves were preferred by 54% over one piece gloves 46%. If gloves are two piece, smooth sleeves are preferred by 86% over pleated sleeves 14%.

Glove replacement period data is in Figure 17 with some

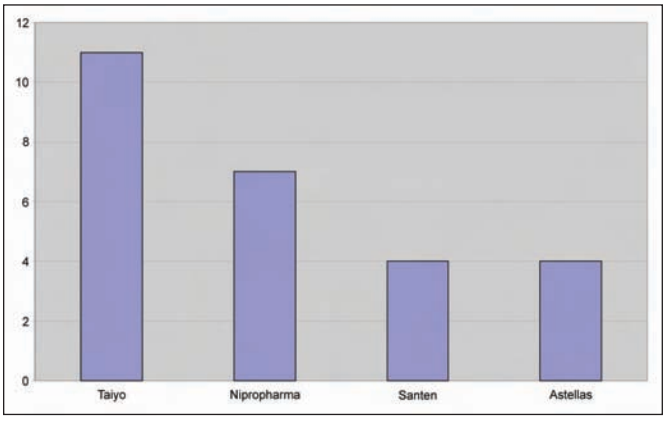


Figure 6. Barrier isolator filling lines – companies with highest usage (Asia only).

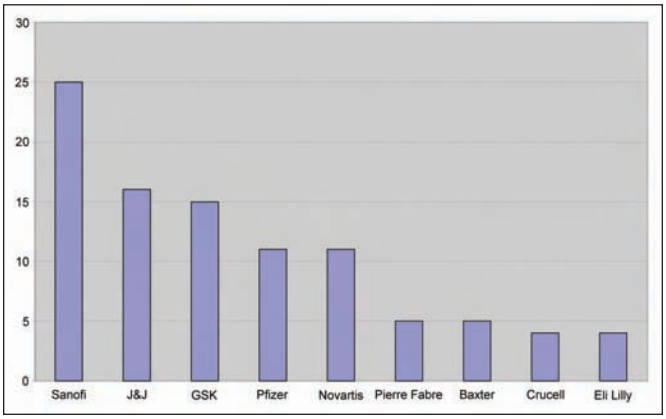


Figure 7. Barrier isolator filling lines – companies with highest usage (Europe only).

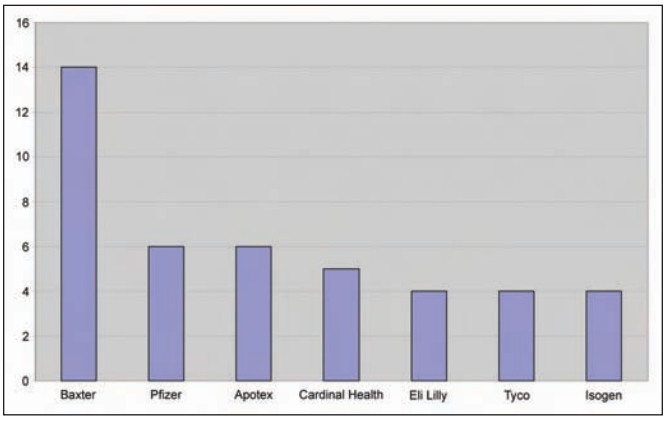


Figure 8. Barrier isolator filling lines – companies with highest usage (North America only).

1998	2000	2002	2004	2006	2008
32	56	67	83	84	99

Table E. Number of companies using barrier isolation.

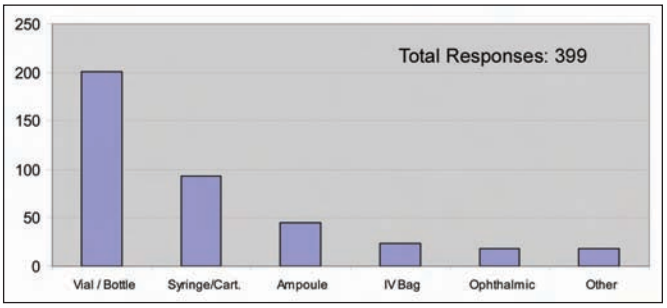


Figure 9. Container type.

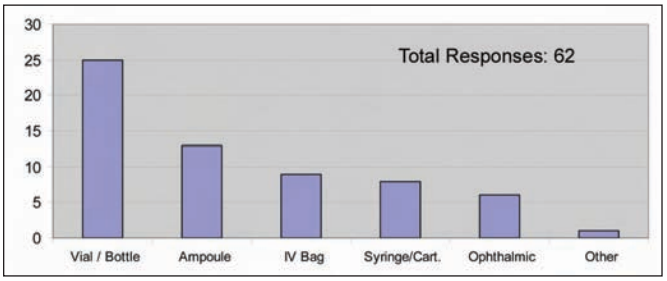


Figure 10. Container type (Asia only).

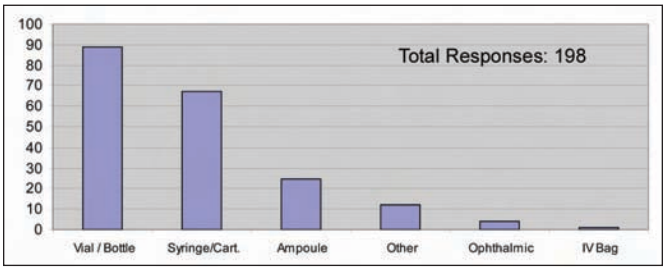


Figure 11. Container type (Europe only).

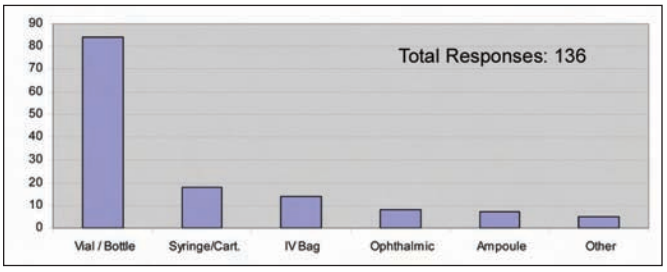


Figure 12. Container type (North America only).

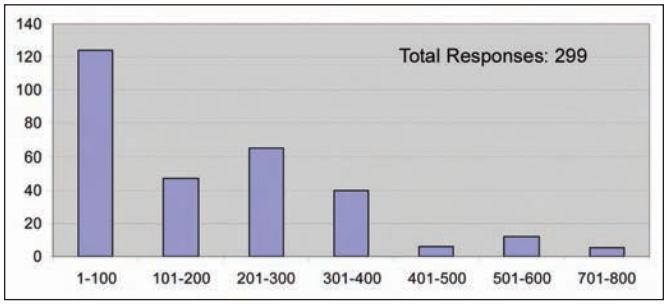


Figure 13. Maximum speed.

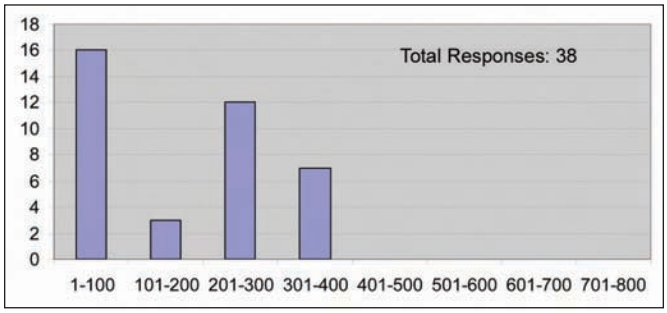


Figure 14. Maximum speed (Asia only).

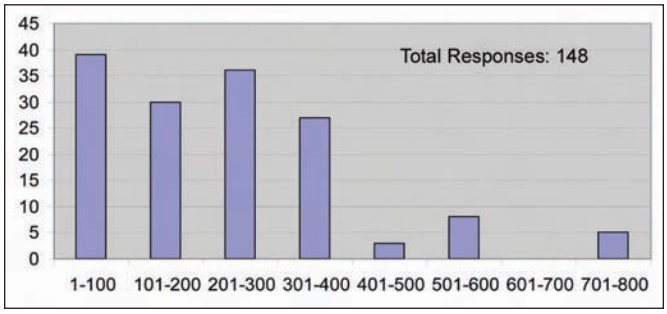


Figure 15. Maximum speed (Europe only).

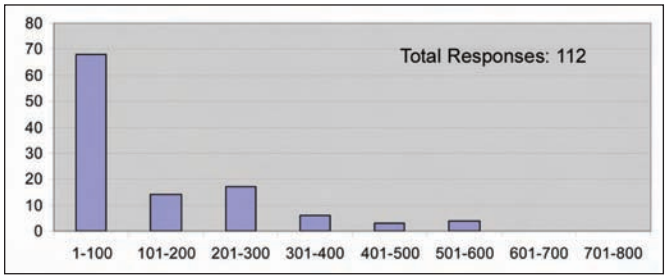


Figure 16. Maximum speed (North America only).

companies able to use gloves up to six months. Method of integrity testing gloves is shown to be predominantly by pressure decay - *Figure 18*. Visual inspection also should be done. 89% of responses indicated usage of a second thin glove with the glove port (typically placed on the hand prior to entering the glove port).

Continued on page 54.

Positive overpressure is typically used in these applications. The concept of "more is always better" does not apply to systems with mouse holes at exits or depyrogenation tunnels that are interfaced with the isolator. Too much overpressure can "blow" the tunnel hot zone air into the washer and melt many parts. Small vials can be blown out of mouse holes destroying the product. Figure 19 indicates that the majority of applications operate between 21 and 40 pascals or ~.1 to .2 inches of water over pressure.

Tunnel sterilizable cool zone technology was used by 65% of those responding.

Containment was a requirement on 42% of total responses over the six surveys. The data with this question must be looked at on a survey by survey basis to look at percent of containment needed on these responses for a two year period. Since 2006, **100%** of 2008 responses indicated a containment need.

Those that indicated that they campaigned product fills within one isolator sterilization event made up 59% of responses. Figure 20 shows the length of campaign from the responses. The maximum campaign length is 28 days.

Finally, cumulative deliveries of isolators are shown in Figure 21. We believe that isolator usage is increasing even faster than shown at the time of writing this article based on equipment manufacturers comments. Data was gathered in first quarter 2008 and the 2009 increase will be much larger than shown here. 2009 data counted was only for what was ordered by first quarter 2008 for delivery in 2009. Many more lines were ordered for 2009 after the data was collected. The dotted line indicates a change in slope after 2004.

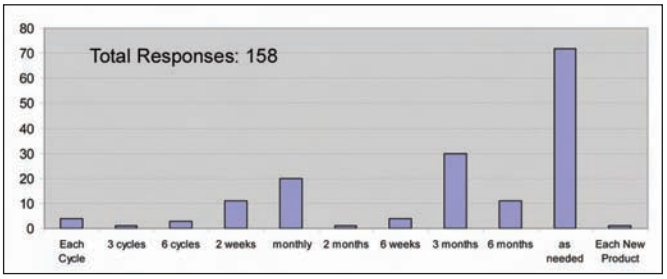


Figure 17. Glove replacement period.

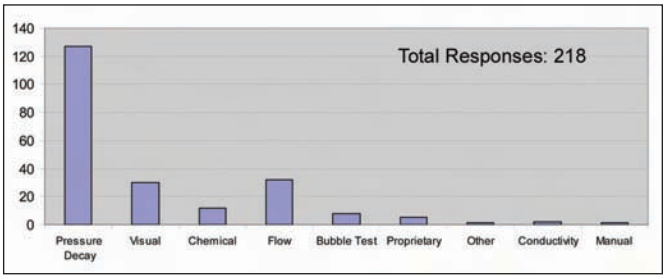


Figure 18. Method for integrity testing of gloves.

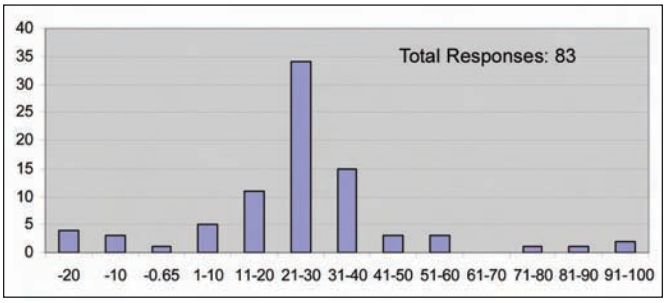


Figure 19. Pressure to washer rooms (12.5 Pascals = .05" Water).

The Trends and Conclusions are:

- Worldwide increase in filling line isolators continues (391) with significant increase in Europe (50) from 2006.
- Asia (9) and North America (28) showed growth in two years.
- Isolators are embraced by some companies and avoided by others.
- Mergers and facility consolidation impact the number of user companies.
- Number of reported isolator lines in operation increased (230 to 283) in two years.
- Vials continue to be the predominant container.
- Hard wall isolators continue to be the preference.
- Smooth sleeve gloves are even stronger than in 2006 (86%).
- Slight preference for two piece gloves (54%).
- Use of a thin second glove is very strong (89%).
- Use of depyrogenation tunnels with sterilizable cool zone increased (65%).

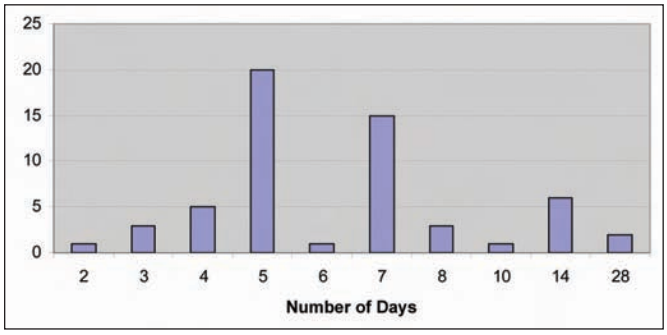


Figure 20. Campaign products (longest run).

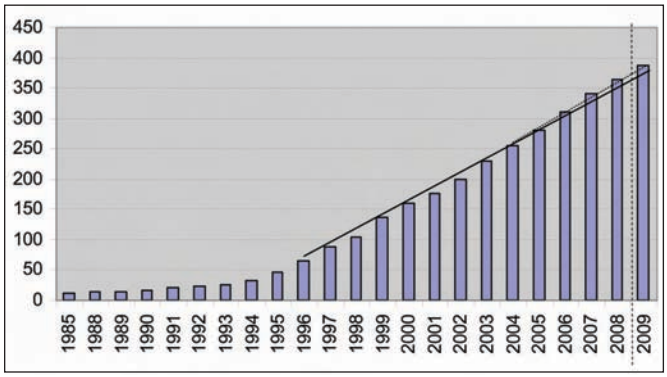


Figure 21. Barrier isolator filling line – cumulative deliveries (2009 is partial data).

- Containment need is increasing (42%) (100% in last two years).
- Campaigning is increasing (59%).

Benchmarking information for those companies investigating the use of isolators is shown below (strongest preferences from survey):

- hard wall isolator; stainless steel and glass
- biodecontamination technology using hydrogen peroxide vapor
- ISO 8 in operation surrounding room classification
- gloves only, meaning minimize use of half-suits for interventions
- two piece gloves with smooth sleeves
- use of a thin second glove
- doing glove integrity tests with pressure decay test (plus visual)

Capital equipment technology and the accompanying depreciation expense last a long time. Remember that today's decisions will impact the company for 15 to 25 years. Look at what is in the pipeline for R&D to make a decision that will cover future products. Many product candidates will have the need of aseptic processing and containment in order to protect both operators and product.

* The author may be contacted for questions or comments by telephone: +1-952-546-2082 or by email: jlysfjord@Q.com.

This article presents the 2007 final data of a survey conducted on the use of RABS for automated fill/finish operations for aseptically filled injectable drugs.

Restricted Access Barrier System (RABS) History and Trends – 2007 Final Data

by Jack Lysfjord and Michael Porter

The authors have done surveys on the use of barrier isolator technology in 1998, 2000, 2002, 2004, and in 2006. These surveys are an attempt to "benchmark" the pharmaceutical industry on a global basis and to look at the historical data and the trends. The data is for automated fill/finish operations for aseptically filled injectable drugs. Manual operations and hand filling and closing in a glove box are not considered. In 2004, a question was asked if it would be possible to get the same type of information for RABS since there seemed to be a great deal of interest in this technology. Due to the energy required to do each survey, the best fit was on the alternate years 2005 and 2007. The 2004 isolator and 2005 surveys were presented in conferences, but not published. The 2005 RABS data points are presented here along with the RABS data from 2007.

RABS is a spin off from isolators. Pfizer, Kalamazoo Michigan (previously Upjohn) in 1992 coined the term RABS for "Restricted Access Barrier System." Their goal was to reduce the contamination risk to a product when filled in a conventional cleanroom situation using existing process equipment. The solution was to create a hard wall barrier with glove ports and transfer ports for stoppers to separate the operator from the critical zone or filling closing zone. This barrier sat in a cleanroom which was class 100 (ISO 5) in operation with full ceiling HEPA filters that generated unidirectional airflow on both the outside and inside of the barrier. The top of the barrier was approximately six inches below the HEPA filters and extended below the filling stoppering machine table top with a three inch air gap to the table top for air to flow out of the barrier with no pressure differential. The doors were physically locked to prevent any interventions. The operator to product separation was by a hard wall barrier together with air flow with no pressure differential – the first RABS.

Isolators provide separation between the operator and product with a hard wall barrier and pressure differential.

The first RABS was a "Passive RABS." There also is "Active RABS" and "Closed RABS" today. Figures 1 to 3 depict types of RABS.

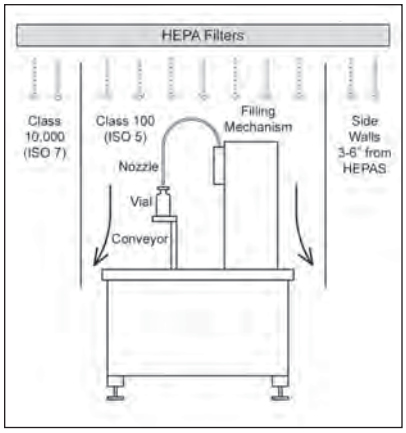


Figure 1. Passive RABS.

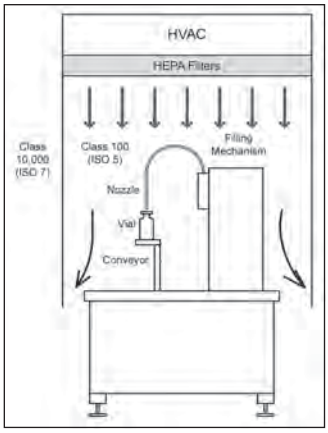


Figure 2. Active RABS.

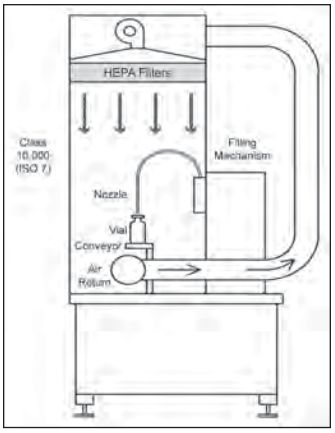


Figure 3. Closed RABS.

The use of a RABS implies more than the enclosure since the following must be in place for the concept of separation with air flow to be successful and reduce the contamination risk to the product:

- properly designed equipment
- management oversight
- a quality system
- proper surrounding room design (ISO 7 minimum)
  - ISO 5 annex for open door interventions
- proper gowning
- proper cGMP training
- initial high level disinfection with a sporicidal agent
- proper SOP for **rare** allowed interventions
  - disinfection (non sporicidal)
  - line clearance
  - documentation of the event

Year	Asia	Europe	North America	TOTAL
2005	12	40	23	75
2007	23	63	38	124

Table A. Number of RABS units.

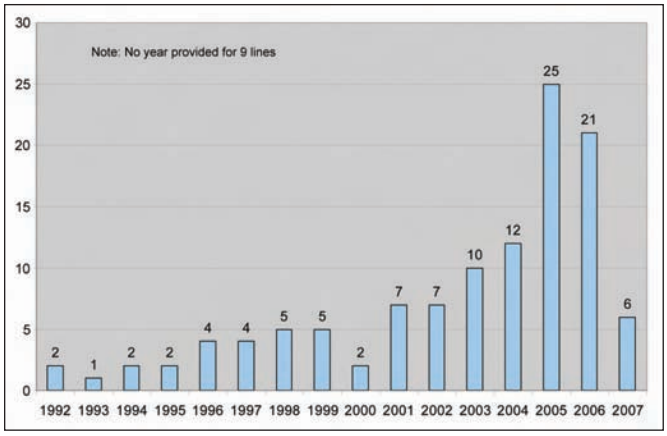


Figure 4. Number of RABS units delivered by year.

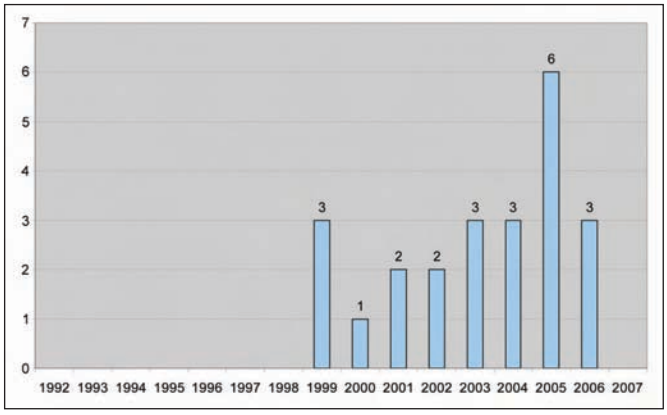


Figure 5. Number of RABS units delivered by year (Asia only).

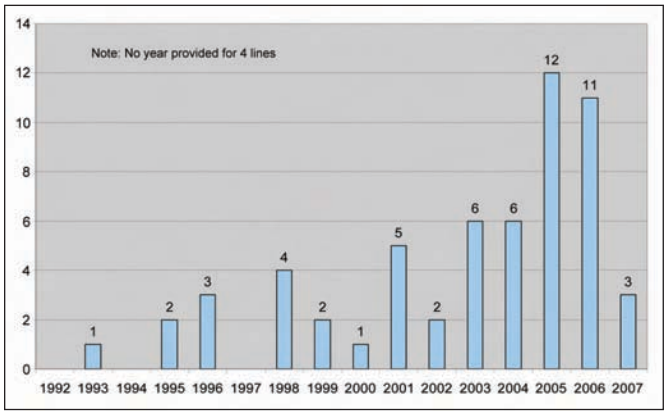


Figure 6. Number of RABS units delivered by year (Europe only).

The S in RABS is for "SYSTEM" and without the systems and procedures above, a simple enclosure is not a RABS and can result in increasing the risk to the product.

In 2005, Stewart Davenport from Pfizer, Kalamazoo, Michigan (part of the team that developed the first RABS) and Joerg Zimmermann from Vetter, Ravensburg, Germany, presented data on cumulative RABS lines media fills from both companies. Each had media fill data that were over one million media fills with no unexplainable positives. They both use the philosophy of never opening the doors of their RABS yielding data equivalent to media fill data of isolators. That is impressive. Here is the survey of RABS history and trends for 2007.

We found 124 RABS in the 2007 RABS survey. Table A gives 2005 and 2007 data and the breakout between Asia, Europe, and North America.

Continued on page 58.

The number of RABS delivered by year overall and the three region breakout are shown in Figures 4 to 7. The types of RABS, passive, active, and closed, are described in Table B. RABS operating philosophy- never opened, limited open, and frequent open responses are shown in Table C. The alarming piece of data indicates many systems (17 companies) frequently open the doors of their RABS.

A listing of the companies with the highest RABS usage is shown in Table D. In 2005, 28 companies had RABS. In 2007, the number increased to 36. In 2005, 25 RABS lines were reported in operation. 36 were in operation in 2007.

Table E shows the RABS lines and the container types that

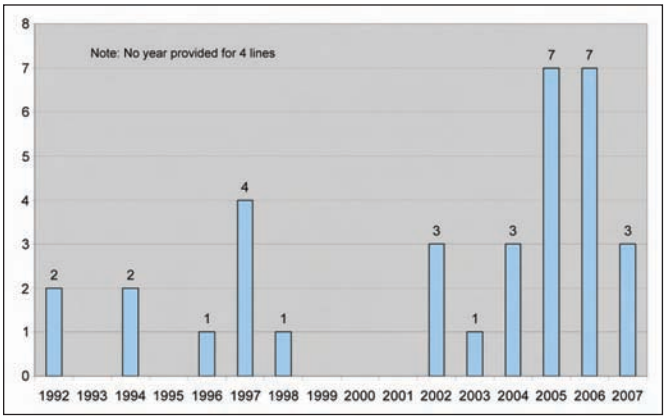


Figure 7. Number of RABS units delivered by year (North America only).

Year	Passive	Active	Closed	TOTAL
2005	16	25	17	58
2007	35	52	39	126

Table B. Types of RABS.

Year	Never Opened	Limited Open	Frequently Open	TOTAL
2005	22	29	1	52
2007	31	48	**17**	96

Table C. Philosophy for using RABS.

	2005		2007	
#	Company	# of Rabs	Company	# of Rabs
1	Vetter Pharma	10	Vetter Pharma	10
2	Pfizer	7	Pfizer	10
3	Aventis	5	GSK	7
4	GSK	4	Aventis	5

Table D. Top 4 companies with RABS.

	2005	2007
Vial/Bottle	48	77
Ampoule	8	12
Syringe/Cartridge	18	29
Ophthalmic	2	5
IV	0	0
Other (including BFS)	0	2
TOTAL Responses	**76**	**125**

Table E. Types of containers processed in RABS.

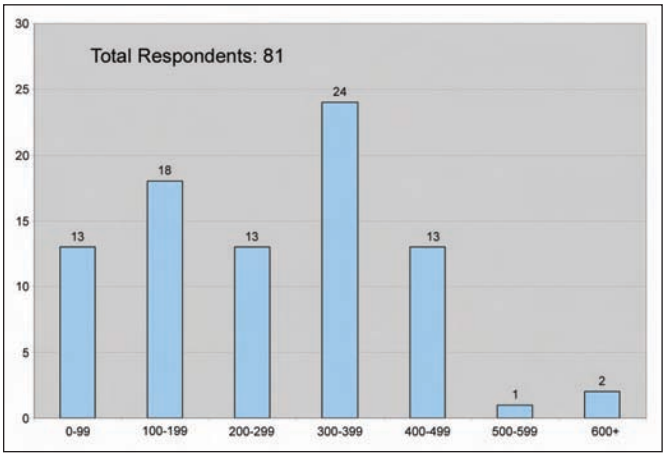


Figure 8. Maximum line speed/minute.

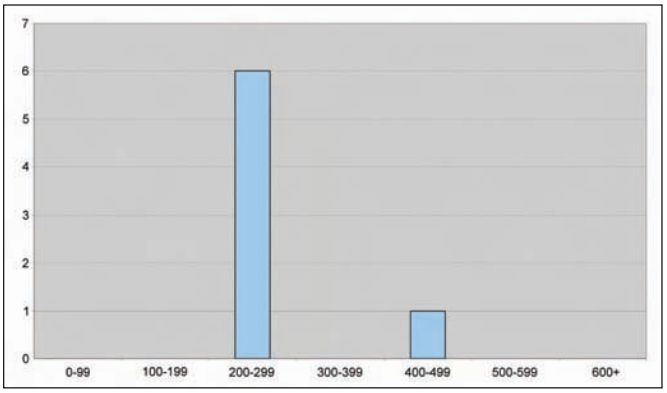


Figure 9. Maximum line speed/minute (Asia only).

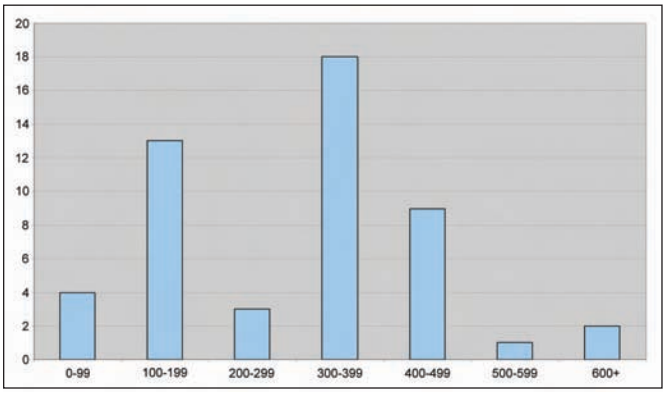


Figure 10. Maximum line speed/minute (Europe only).

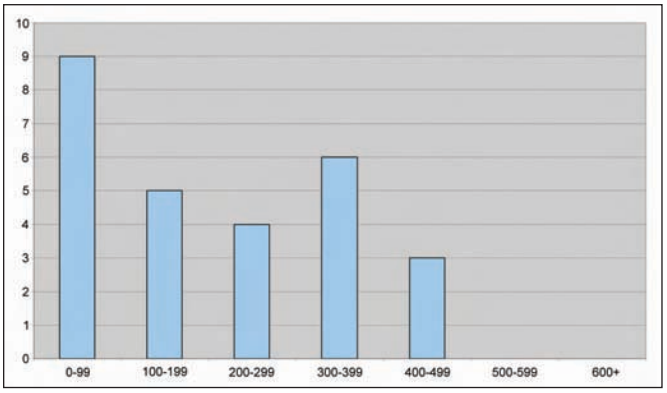


Figure 11. Maximum line speed/minute (North America only).

Year	Autoclave	Sanitize in Place	Other	TOTAL
2005	16	11	4	31
2007	16	21	12	49

Table F. Method of sanitizing gloves.

Year	Yes	No	TOTAL Respondents
2005	29	0	29
2007	31	7	38

Table G. Second inner glove used.

	2005	2007
Each Cycle	4	3
Every 5 Runs	1	1
Every 15 Cycles	10	10
Every 6 Weeks	1	1
Every 3 Months	4	4
Every 6 Months	0	1
As Needed	8	18
TOTAL Responses	**28**	**38**

Table H. Glove replacement time.

	2005	2007
Pressure Decay	20	20
Visual	4	18
Other	2	2
None	1	1
TOTAL Responses	**27**	**41**

Table I. Glove test method.

	2005	2007
Active Oxygen Agent		10
Gas Formaldelhyde		10
Spor Klenz	0	6
Chemical Agent and Formaldehyde Gas	5	5
Peracetic Acids	3	3
Chemica Agent and VHP Gas	2	2
Decon Quat 100	2	2
Germex B12, Apesin AP3, Apesin Rapid	2	2
IPA		2
Rotating Disinfectant Regime		2
2 Phenols + IPA	1	1
Bleach/Detergent		1
Disinfectant Medium Level		
Alkalidetergent High Level		1
Hydrogen Peroxide	1	1
Hypochlorite 5%	2	1
Liquid Disinfectant	1	1
Same as Room Sanitizers, typical		1
Vesphene, LPH	1	1
VHP Gas	1	1
Alcohol 70%, decon. clean	1	
TOTAL Responses	**28**	**38**

Table J. Types of sanitizing agents.

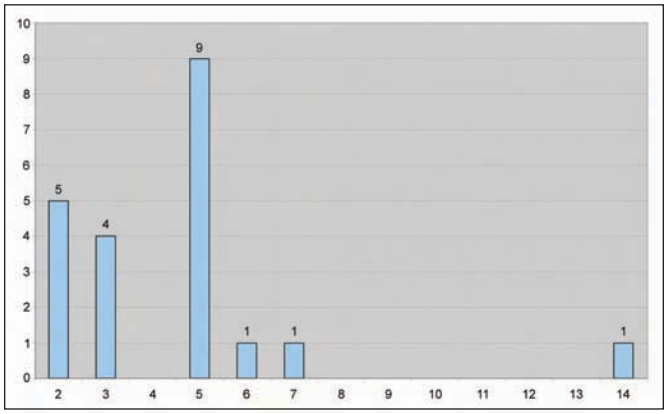


Figure 12. Number of days line campaigned.

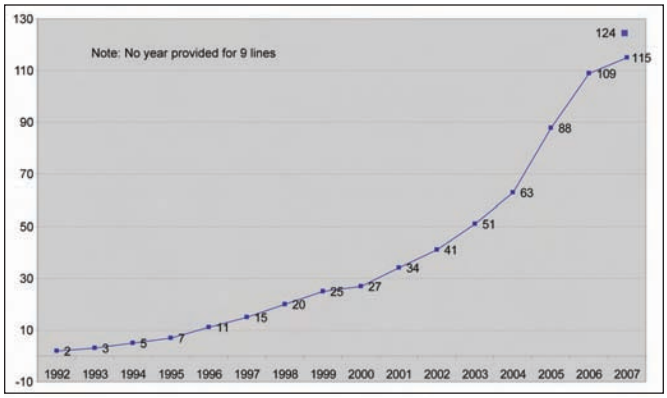


Figure 13. RABS.

they process. Figure 8, 9, 10, and 11 lists frequency of RABS use by maximum line speed in total and then breakouts for the three regions.

Glove data is listed in Tables F, G, H, and I. The types of sanitizing agents used are listed in Table J.

When RABS lines campaign product, the length of campaign in days and frequency are displayed in Figure 12. Six of the responses indicated a need for containment of potent product to protect the operator.

Figure 13 displays the cumulative use of RABS and how the rate of delivery has jumped since 2003. Note that nine responses did not indicate year of delivery to get total to 124 units. In summary:

- RABS use is increasing globally.
- Europe is ahead of North America-similar to isolator data.
- Asia started later, but is increasing in use of RABS.
- RABS is an option to consider to improve asepsis particularly with retrofits.
- Frequent opening of doors on the barrier is a big caution area since it will compromise asepsis. If this is the routine mode of operation, it is not a RABS.

* The author may be contacted for questions or comments by telephone: +1-952-546-2082 or by email: jlysfjord@Q.com.

US FDA Speakers Figure Prominently at ISPE's 2009 Washington Conference

Numerous regulators from the US Food and Drug Administration (US FDA) were featured speakers at the ISPE 2009 Washington Conference – Engineering Regulatory Compliance, that took place at the JW Marriott in Washington, DC, USA, 1 to 4 June 2009.

Speaker information – along with seminar agendas and training course outlines – for the four-day event are available on the ISPE Web site and include the following listings:

- Richard Friedman (Director, Mfg. and Product Quality, CDER), Tara Gooen (Chemical Engineer, CDER), Robert Sausville (Supervisory Consumer Safety Officer, CBER), and Joyce Rockwell (Consumer Safety Officer, CBER) were featured US FDA speakers at the 18th Annual Barrier Isolation Technology Forum: Innovation Updates and New Case Studies.

- Helen Winkle (Director, Office of Pharmacy, CDER), Christine Moore (Deputy Director, CDER), and Sharmista Chatterjee (Staff Fellow/Reviewer, CDER) were featured US FDA speakers at the PQLI®: Science, Regulatory, Manufacturing, and Engineering Working Together for Global Realization and Implementation of the ICH Quality Vision seminar. Joseph Famulare (Deputy Director, Office of Compliance, CDER), Richard Friedman (Director, Mfg. and Product Quality, CDER), Vibhakar Shah (Consumer Safety Officer, CDER), Elaine Morefield (Supervisory Chemist, CDER), Grace McNally (Senior Compliance Officer, CDER) and Patrick Swann (Deputy Director, Division of Monoclonal Antibody, CDER) of the US FDA were invited, as well.

- Ilisa Bernstein (Sr. Advisor Pharmacist, CDER) and Steven Silverman (Regulatory Counsel, CDER) were featured US FDA speakers at the Global Supply Chain Integrity and Anti-Counterfeiting seminar. A representative from the FDA's Office of Policy and Program Planning, CDER also was invited to speak.

- Barry Rothman, Consumer Safety Officer for the FDA's Division of Manufacturing and Product Quality, CDER was invited to speak at the Current and Future Packaging Challenges for Investigational Products seminar.

- H. Gregg Claycamp, PhD, the Associate Director of Risk Analysis and Strategic Policy Assessment, CVM was the featured FDA speaker at the Applied Risk Management – Addressing Cross Industry Challenges seminar.

- Malcolm Oliver, GMP Inspector for the MHRA, was invited to speak at the Commissioning and Qualification (C&Q): Practical Applications of Science and Risk-based Approaches to Validation seminar, along with several confirmed leaders of the pharmaceutical manufacturing industry.

- As an additional resource on the topic of C&Q, there was a live Webinar 5 May 2009 on Implementing the ASTM Standard for Verification (C&Q).

There were also seminars devoted to GAMP and facility renovation, as well as two-day training courses. They are:

- GAMP® Good Practice Guides: Validation of Process Control Systems (VPCS), and Calibration Management, A Risk-Based Approach

- Extreme Facility Makeover: Successful Path to Facility Renovation and Retrofit

- Training – Basic Principles of Computerized Systems Compliance

- Training – Applying the GMPs

For upcoming ISPE Education and Training information, visit www.ISPE.org or call ISPE Members Services at tel: +1-813-960-2105.

ISPE Korea Affiliate in Development

The Korea Affiliate, the newest affiliate to join ISPE's family, is well under way in its development. The Korea Affiliate will be located in South Korea, officially the Republic of Korea and often referred to as Korea.

INTERPHEX Keynote Message: Industry Needs to Reinvent Itself

by Rochelle Runas, ISPE Technical Writer

Expiring patents. An economic slump. New technologies. Regulatory agencies becoming increasingly risk averse. A new administration in Washington.

In a world today that faces these and other uncertainties, one thing's for sure: The pharmaceutical industry needs to reinvent itself, whether it likes it or not.

That was a main message of this year's Keynote at Interphex NY, delivered Tuesday, 17 March at the Jacob Javits Convention Center in New York, New York. The keynote included a presentation by G. Steven Burrill, CEO, Burrill & Co., who shared his vision of the future of healthcare and overriding trends affecting the global industry.

Burrill said the industry will be facing stricter regulatory oversight; the need to prove drug safety and comparative effectiveness (this third standard will begin to emerge); generic biopharmaceuticals, biosimilars; an increase in stem cell funding; and an increase in healthcare IT funding.

So, in 2020, what will the healthcare delivery system look like? Burrill said in the last 2000 years, the pharmaceutical industry has not really changed; people got diseases and they were treated. But, this is not going to be true in the next five to 10 years.

We are changing the nature of the healthcare equation, moving away from a treatment-based system with a one size fits all mentality toward late stage detection and intervention, and a prevention- and wellness-based system. "We've lived in a world of blockbusterology and we're going to live in a world of more targeted, personalized medicines."

Burrill said he envisions a consumer driven healthcare world that includes concepts such as genetic screening, web-based diagnostics, patient-centric self care, and Wal-Mart-like health centers operated by nurse practitioners. Medical tourism will become more popular. For example, it is becoming cheaper to send a patient in need of a hip replacement on a plane to India and put them up in the Four Seasons, than getting the procedure done in local hospital, Burrill said.

What does this kind of world mean to the pharmaceutical industry? According to Burrill, big pharma will disintegrate, a trend already demonstrated by big company mergers. Low margin

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

INTERPHEX Keynote Message

Continued from page 62.

ethical drugs will predominate (China, India, and other low cost manufacturing sites will have an edge). International regulatory agencies will collaborate.

Big pharma today, which is vertically integrated (R&D, manufacturing, distribution, etc.) will disintegrate to be horizontally integrated. The "virtual pharma company" will emerge, with operations located at different sites. Capital will go to where the best opportunities are and partnerships will continue, said Burrill. Also, diseases will have no boundaries, so all companies big and small will be global from day one.

The presentation was followed by a panel discussion with Burrill; Timothy Moore, Senior Vice President, Global Supply Chain, Genentech; Divakar Ramakrishnan, PhD, Executive Director, Manufacturing Science and Technology, Eli Lilly & Co.; and Michael Kowolenko, PhD, Senior Vice President, Biotech Operating Unit, Technical Operations and Product Supply, Wyeth Pharmaceuticals. The panel discussed how they are handling today's challenges.

"We try to balance cost and risk," said Moore. "We put a lot of emphasis on managing risk in our supply chain, balancing the amount of inventory to carry vs. patient need."

Ramakrishnan said his company greatly emphasizes six sigma programs and efficiency.

In the end, biology and technology will be more important than concrete, said Kowolenko.

JPI Features Article on PQLI Legacy Products

The March 2009 issue of the *Journal of Pharmaceutical Innovation*, available online to Members only, features the following articles:

- PQLI®: Current Status and Future Plans
  by John C. Berridge
- PQLI Application of Science- and Risk-based Approaches (ICH Q8, Q9, and Q10) to Existing Products
  by Chris Potter
- Investigation of the Statistical Power of the Content Uniformity Tests Using Simulation Studies
  by Phillip D. Lunney and Carl A. Anderson
- Aqueous Solubility Enhancement Through Engineering of Binary Solid Composites: Pharmaceutical Applications
  by Michael D. Moore and Peter L. D. Wildfong

ISPE Members can access JPI by visiting www.ISPE.org/JPI.

Classified Advertising

Architects, Engineers – Constructors

CRB Consulting Engineers, 7410 N.W. Tiffany Springs Pkwy., Suite 100, Kansas City, MO 64153. (816) 880-9800. See our ad in this issue.

Parsons, 150 Federal St., Boston, MA 02110. (617)-946-9400. See our ad in this issue.

Cleanroom Products/Services

AES Clean Technology, 422 Stump Rd., Montgomeryville, PA 18936. (215) 393-6810. See our ad in this issue.

Plascore, 615 N. Fairview, Zeeland, MI 49464. (800) 630-9257. See our ad in this issue.

Dust Collectors

Farr APC, 3505 S. Airport Dr., Jonesboro, AR 72401. (866) 530-5474. See our ad in this issue.

Employment Search Firms

Jim Crumpley & Associates, 1200 E. Woodhurst Dr., Bldg. B-400, Springfield, MO 65804. (417) 882-7555. See our ad in this issue.

Robert Drexler Associates, Inc., PO Box 151, Saddle River, NJ 07458. (201) 760-2300. See our ad in this issue.

Instrumentation

Hach Ultra Analytics, 5600 Lindbergh Dr., Loveland, CO 80539. (970) 663-1377. See our ad in this issue.

Passivation and Contract Cleaning Services

Active Chemical Corp., 4520 Old Lincoln Hwy., Oakford, PA 19053. (215) 676-1111. See our ad in this issue.

Cal-Chem Corp., 2102 Merced Ave., South El Monte, CA 91733. (800) 444-6786. See our ad in this issue.

Processing Systems

GEA Niro Pharma Systems, 9165 Rumsey Rd., Columbia, MD 21045. See our ad in this issue.

Optima Machinery Corp., 1330 Contract Dr., Green Bay, WI 54304. See our ad in this issue.

Pumps

Wilden Pump & Engineering, 22069 Van Buren St., Grand Terrace, CA 92313. (909) 422-1730. See our ad in this issue.

Rupture Discs

Fike Corp., 704 SW 10th St., Blue Springs, MO 64015. (816) 655-4546. See our ad in this issue.

Sterile Products Manufacturing

Process Tek - *Sterility by Design*
INNOVATION, RELIABILITY & PROFESSIONALISM
R&D, Validation, GMP Auditing,
HACCP, Problem Solving and Training
for sterile products, packages & processes
Kailash S. Purohit, PhD
www.processtek.net • kaipurohit@processtek.net

Temperature Control Systems

Budzar Industries, 38241 Willoughby Pkwy., Willoughby, OH 44094, (440) 918-0505. See our ad in this issue.

Validation Services

Commissioning Agents, Inc., 1515 N. Girls School Rd., Indianapolis, IN 46214. (317) 710-1530. See our ad in this issue.

Valves

Gemu GmbH & Co., Fritz-Mueller-Str. 6-8, D-74653 Ingelfingen, Germany. +49 7940123-0. See our ad in this issue.

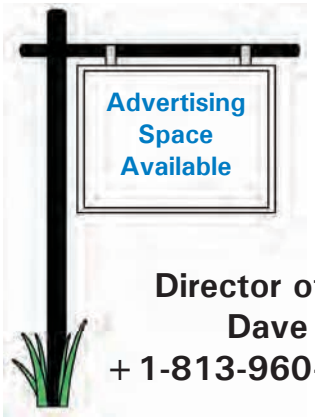
Vial Traying Systems

Hurst Corp., Box 737, Devon, PA 19333. (610) 687-2404. See our ad in this issue.

Water Treatment

Elettracqua Srl, Via Adamoli 513, 16141 Genova, Italy. +39 0108300014. See our ad in this issue.

MECO, 12505 Reed Rd., Suite 100, Sugar Land, TX 77478. (800) 421-1798. See our ad in this issue.



Call ISPE
Director of Sales
Dave Hall at
+1-813-960-2105.

Inc. 1955

ACTIVE CHEMICAL CORP.

SPECIALISTS IN . . .

— LABORATORY CONTROLLED —

- CHEMICAL CLEANING SERVICES OF HEAT EXCHANGE EQUIPMENT
- PASSIVATION OF STAINLESS STEEL PIPING
- STERILIZATION OF PIPING & EQUIPMENT
- SOFTENERS & DEIONIZERS
- RECONDITIONING OF FILTERS & ION EXCHANGERS
- WATER TREATING CONSULTANTS
- BOILER & COOLING WATER CHEMICALS

SERVICE CONTRACTS

(215) 676-1111

4520 Old Lincoln Hwy., Oakford, PA 19053

FDA

Division Director Position

U.S. Department of Health and Human Services / Food and Drug Administration

SUBMIT RESUME TO:

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of New Drug Quality Assessment (ONDQA)
ATTENTION: Erik Henrikson
10903 New Hampshire Ave., Bldg. 21 Rm. 2669
Silver Spring, MD 20993-0002

For additional questions please call 301-796-4110

The Food and Drug Administration is recruiting a Division Director for the Office of New Drug Quality Assessment (ONDQA), Office of Pharmaceutical Science, Center for Drug Evaluation and Research. The mission of ONDQA is to assess the critical quality attributes and manufacturing processes of new drugs, establish quality standards to assure safety and efficacy, and facilitate new drug development. Strong organizational and executive leadership skills are very desirable. The Division Director is responsible for providing scientific direction and for planning, managing, and organizing pharmaceutical quality assessment of drug products assigned to the division to ensure safety, purity, potency and effectiveness.

DESIRED QUALIFICATION: A Ph.D. degree in chemistry and/or other related disciplines (e.g., biochemistry, pharmaceutics, industrial pharmacy, engineering), with appropriate experience in pharmaceutical development, manufacturing, and regulations, is desired. Candidates for Civil Service must be U.S. citizens. Graduates of foreign colleges/universities must provide proof of U.S. education equivalency.

SALARY RANGE: Civil Service GS-15 at $120,830 to $153,200 per annum with an excellent benefits package and training opportunities. For an exceptionally qualified and experienced candidate, additional compensation may be provided

THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION IS AN EQUAL OPPORTUNITY EMPLOYER AND HAS A SMOKE FREE ENVIRONMENT

ACTIVE CHEMICAL 65
AES CLEAN TECHNOLOGY 27
BUDZAR INDUSTRIES 39
CAL-CHEM CORP. 37
COMMISSIONING AGENTS 25
CRB CONSULTING ENGINEERS 3
JIM CRUMPLEY & ASSOCIATES 64
ELETTRACQUA 13
EMERSON PROCESS MANAGEMENT 9
ENDRESS + HAUSER 67
FOOD AND DRUG ADMINISTRATION/CDER 65
FARR AIR POLLUTION CONTROL 2
FESTO 45
FIKE CORP. 29
GEA PROCESS ENGINEERING 47
GEA WESTFALIA SEPARATOR 55
GEMU GMBH 63
GLATT GMBH 17
HACH COMPANY 43
HOWORTH AIR TECHNOLOGY 19
HURST CORP. 57
IMA ACTIVE 53
IMA LIFE 35
INTELLIGEN 23
INTERPHEX365 49
MECO 11
NNE PHARMAPLAN 68
OPTIMA MACHINERY 31
PARSONS 5
PHARMACEUTICAL ONLINE 62
PLASCORE 15
QPHARMA 7
TELSTAR 41
WILDEN PUMP & ENGINEERING 51

ENGINEERING PHARMACEUTICAL INNOVATION ISPE

ISPE Brussels Conference Highlights

The ISPE Brussels Conference welcomed more than 180 delegates to update their knowledge and to network at Sheraton Brussels Hotel in Brussels, Belgium on 30 March to 2 April 2009. This year's conference offered a variety of new and enhanced opportunities for attendees to take advantage of. Some of the highlights from the conference were:

- Live webinar presentation from Nick Haycocks in California, USA on the HVAC Good Practice Guide and Good Engineering Practice, as well as the Environmental Cleanliness Classification Quiz that generated lots of discussion at the seminar Heating, Ventilation and Air Conditioning (HVAC): Good Practice and Innovations.

- Regulatory aspects of continuous processing were presented by Dr. Moheb Nasr, Director, Office of New Drug Quality Assessment and Joe Famulare, Deputy Director, Office of Compliance, FDA at the seminar Continuous Processing and Process Intensification for APIs, BPCs and Excipients. Part of the program was developed in conjunction with the International Pharmaceutical Excipients Council (IPEC) since, for the first time, the seminar considered not only APIs/BPCs, but excipients, as well. Delegates were also introduced to the forthcoming ISPE white paper on regulatory issues for continuous processing.

- In a change from the normal format, a one-day interactive Project Management Workshop was held on developing lean, agile project plans. Delegates were working on a detailed project plan over the course of three exercises and received templates as part of the conference documentation allowing them to put them into practice back at the job.

- Andrew Cochrane, UK regulator from MHRA, provided a very useful overview of the current status of the revision of Annex 11 during the seminar GAMP® 5: Part 11, Annex 11 and Industry Hot Topics. The seminar included an interactive workshop on Maintaining Control of Operation, as well as Quality Risk Management in Process Automation, where the links between ICH Q9 and the GAMP® 5 QRM approach were explored. Two new groups were formed during the seminar: a GAMP SIG on outsourcing/offshoring topic, as well as a local GAMP Benelux group with an interactive day of workshops coming up.

- A live webinar presentation was given by Cameron Sipe in the US on the update to the ISPE Water and Steam Baseline® Guide during the Critical Utilities seminar.

The Brussels Conference also hosted a sold-out exhibition with a showcase of the latest new tools and solutions.

The next ISPE events in Europe include Madrid Training from 18 to 21 May; Strasbourg Conference held from 28 September to 1 October; and Dublin Training held from 19 to 22 October 2009.

Our focus: your compliance.

Our innovative technologies combined with our understanding of industry requirements and our commitment to work with you ensure your compliance. You can rely on us to thoroughly assess the risks you face and help you optimize your processes and quality system performance. Endress+Hauser: your partner in creating value. www.endress.com/life_sciences

Endress+Hauser
Instruments International AG
Kägenstrasse 2
4153 Reinach/BL1
Switzerland

Phone +41 61 715 81 00
Fax +41 61 715 25 00
info@ii.endress.com
www.endress.com

Endress+Hauser
People for Process Automation

more than engineering

The traditional approach to engineering is not enough to **succeed** in today's market. You require a **focused** partner created from industry DNA who can deliver a **competitive advantage.**

We lead. We deliver. We are more than engineering.

Consulting | Engineering | Construction | Validation | Solutions

NNE Pharmaplan is the world's leading engineering and consulting company focused exclusively on the pharma and biotech industries. NNE Pharmaplan employs more than 1500 people at over 20 locations around the world.

nne pharmaplan®

nnepharmaplan.com