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PDA Letter

Volume XLV • Issue #8

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September 2009

In This Issue:

PDA Parenteral Drug Association

Connecting People, Science and Regulation®

ICH Q7: A Worldwide Guide

A look back at nearly a decade of GMPs for APIs

*In July, PDA Letter Editor **Walter Morris** was able to speak with two members of the ICH Q7 Expert Working Group about the impact of the document nearly a decade after it was finalized: **Edwin Rivera-Martinez,** U.S. FDA and **Gordon Munro,** Watson Pharmaceuticals. The interview is presented below in Q&A format, with the initials PL, GM and ERM used to indicate the PDA Letter, Gordon, and Edwin, respectively. View this article at www.pda.org/pdaletter to read additional questions and answers not included in the print edition. **Note:** Gordon Munro expresses his thoughts and opinions in this interview, and his comments should not be construed as the official opinion of Watson Pharmaceuticals, Inc. or its affiliates.*

PL: First off, thanks to both of you for participating in this interview. ICH Q7 has been in effect for not quite a decade yet, but the first version, or Step 2 document, was published in 1999, so the industry has been adapting to the guidance for nearly that amount of time.

In your opinion, how has the consumer/patient benefitted from GMPs for active pharmaceutical ingredients over the last ten years?

GM: As far as consumers are concerned, I think they are getting better quality assurance of the active ingredients that go into the medicines that they get. So there should be a greater assurance of the quality, safety, efficacy of the end product, because we are now working with a more standardized approach to the control of the quality of the APIs that go into those products.

ERM: From my perspective, we have greater assurance today of the quality of APIs, because we have a GMP standard subjecting them to greater controls.

Whenever the regulatory authorities go out and conduct inspections, basically, we are all inspecting to the same standard. We didn't have this before Q7. This has resulted in benefits to dosage manufacturers and ultimately to consumers/patients in the medications they take.

PL: This leads us into my next question: benefits to the industry. I can see where you are going—consistency of expectations.

ERM: That is right. Consistency of expectations. Because there is only one standard it is a lot easier for API manufacturers to know what is to be expected of them when undergoing an inspection regardless of the regulatory authority involved, whether it be from the United States, the European Union, Japan, or now even Australia's Therapeutic Goods Administration (TGA) and other regulators

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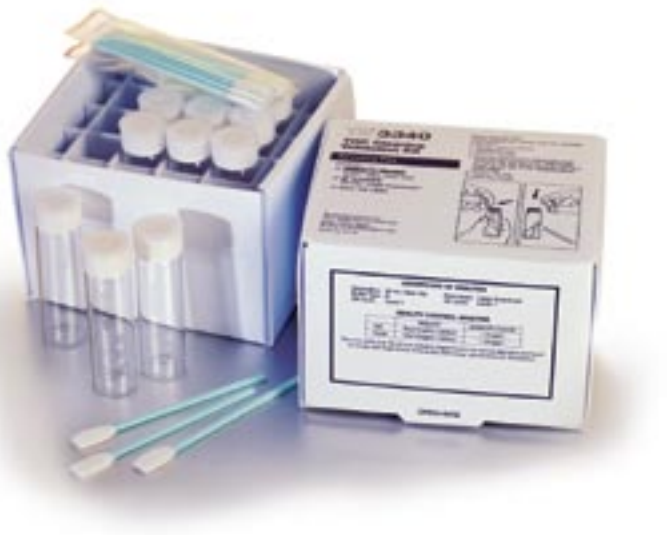

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Cover art:
A "look back" at ICH Q7 shows that the guidance has had a tremendous positive impact on the API segment of the industry, and, most importantly, has helped align regulatory expectations across the globe.

Coming Next Issue:
PDA's Universe of Pre-filled Syringes: Six Years and Running

Editor's Message

The Fruits of Labor Revealed

Conferences, workshops, articles in the trade press and other information outlets, including this publication, spend a great deal of time writing about new laws, regulations, guidances and standards that impact our industry. While the coverage can be in-depth while these various rules and standards progress through their respective lengthy development processes, their *ex post facto* impact is rarely discussed. So, a year ago as the PDA Letter Editorial Committee (PLEC) and the Letter editors discussed the 2009 Editorial Calendar, one of the members said, "Wouldn't it be great to have an article discussing the impact of an ICH guideline a decade later?" And the rest of us agreed. That led us on the path to this issue's cover story "ICH Q7: A Worldwide Guide-A look back at nearly a decade of GMPs for APIs." PDA is very fortunate that busy people like **Edwin Rivera-Martinez** and **Gordon Munro**—both of whom helped draft Q7—take time away from their day jobs to help us out, as both agreed to participate in our Q7 retrospective. I led the interview for PDA and can say that it was a real pleasure talking to two true experts on the subject. Both helped focus the interview on the important aspects of Q7's legacy and how it has been implemented over the last eight years. After speaking with Gordon and Ed, I'm left to wonder if Q7 isn't one of the most successful guidances ever created, considering how many countries and regulatory authorities are using it.

ICH Q7 was not our only target for this issue, as we also conducted numerous interviews on ICH Q6A and Q6B, both of which have been in effect for a decade, but space limitations and deadlines required us to shelve the article for publication in a future issue. I can assure all readers that the article will be worth the wait, so stay tuned!

This issue also includes a thought-provoking commentary by **Martyn Becker**, who returns to our pages with questions about the World Health Organization draft proposal to revise its GMPs for sterile drugs (p. 26).

I've received feedback recently that our "Tools for Success" series in the Membership Section is well-liked, particularly with the hard economic times impacting mostly all of us, so we are happy to offer one this issue called "Finding the Upside in the Economic Downturn" (p. 32). Along the same theme, PLEC member **Anita Whiteford**, who recently began a new career as a university professor, graces our pages again with a look at training in tough times, with "Conducting Effective Training with a Shrinking Budget" (p. 44). We hope you enjoy this edition, and, as always, we hope to hear from you.

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Adrienne Fierro Assumes Vice President of Marketing Role at PDA

PDA would like to welcome **Adrienne Fierro,** Vice President of Marketing Services, to its global headquarters in Bethesda, Md.

Adrienne comes to PDA with over 15 years of marketing experience. Prior to joining PDA, Adrienne gained much experience working for the Food and Drug Law Institute, the American Society for Biochemistry and Molecular Biology, and the American Association of Immunologists.

With her proficient ability, Adrienne has already identified a couple of strategies for PDA: She would like to see PDA further advance itself in a global capacity by enhancing the Association's brand and to promote the message of providing exceptional education and information through the Training and Research Institute and the chapters.

Adrienne joined PDA because of its strong reputation in the industry

While she has been at PDA only a short time, Adrienne said she was impressed with the exceptional culture that exists at PDA, as well as the level of honesty, loyalty and commitment that PDA team members show on a daily basis. "The PDA team is hard-working and committed to advancing PDA. I am honored to be among a group of such knowledgeable and talented people."

"The PDA team is hard-working and committed to advancing PDA. I am honored to be among a group of such knowledgeable and talented people"

Adrienne looks forward to hearing from PDA members and serving their needs in the future. Adrienne can be reached at fierro@pda.org.

PDA Web Seminars

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Upcoming Web Seminars

Sharp Injury Prevention - Update on the European Landscape
September 15, 2009, 1:00 p.m. - 2:30 p.m. (ET)

Among the 35 million health workers worldwide, about three million experience percutaneous exposures to blood borne pathogens each year and many cases remain unreported. This presentation provides an overview of sharps injury risks and prevention measures and will highlight the legislative and regulatory landscape in Europe, including the recent update on political and legislative activities on European national level and on EC level. Furthermore, a brief overview will be presented on ISO standardization activities, related to sharps prevention devices and accessories.

Presented by

William Dierick
Business Development Manager, Global Pharmaceutical Solutions,
Terumo Europe N.V.

Application of Process Analytical Technologies (PAT) for Effective Cleaning Validation Risk Management
September 17, 2009, 1:00 p.m. - 2:30 p.m. (ET)

The validation of cleaning systems and cleaning processes is costly for initial testing and ongoing monitoring and revalidation. Application of PAT to cleaning systems and processes provides tools that can provide real-time assurance of cleaning process operation within validated parameters, thus providing a means for effective, cost efficient, and successful risk assessment and management. Effective strategies and methodologies for implementation of TOC for cleaning system and cleaning process PAT will be presented with respect to assessment and management of risk and the economic advantages of online analysis for a CIP skid.

Keith Bader
Director of Technical and Quality Services
JM Hyde Consulting, Inc.

Single-use Membrane Chromatography: Novel Applications and Regulatory Guidelines
September 21, 2009, 1:00 p.m. - 2:30 p.m. (ET)

Single-use membrane chromatography has gained considerable speed in recent years in biomanufacturing due to a growing bottleneck that lies with downstream processing. As developments in fermentation and cell culture processes lead to increasing titers of therapeutics, clarification and purification schemes must be re-evaluated to accommodate for the higher amounts of product and impurities. As operational costs continue to escalate, companies are also looking at single-use technologies to reduce fixed costs and downtime in their facilities. Membrane chromatography is a promising solution to easing the downstream bottleneck.

Dave Zhou
Associate Product Manager
Sartorius Stedim Biotech

Optimal Cold Chain Management through North American Distribution Networks
September 24, 2009, 1:00 p.m. - 2:30 p.m. (ET)

This cold chain compliance program was applied progressively, globally and site-by-site, to level up the compliance of the Wholesaler's Distribution Network. Furthermore, a cold chain maintenance program was also installed to ensure the sustainability of the cold chain compliance. The implementation of such a cold chain compliance program enables major North American Pharmaceutical Distribution Networks to upgrade cold chain management and to fully comply with the various guidelines for temperature control of drug products during storage and transportation.

Jean Bédard,MBA
Vice-president and CEO
Alternative Technologies Pharma Inc.

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Science & Technology Snapshot

Journal Editorial Team Now in Place

Rich Levy, PhD, PDA

Without doubt, the most exciting developments in PDA's Science and Technology program in 2009 have been the changes to the *PDA Journal of Pharmaceutical Science and Technology*. For readers who have been following the events as we've reported them in the Letter, we hope you don't feel it is overkill, but we cannot emphasize enough just how dramatic the changes are. Last month, we dedicated the cover of the Letter to the naming of new Editor **Govind Rao**, PhD, and the launch of the PDA Journal online. Well, I'd like to use this space this time to provide some additional updates.

Govind has stepped in nicely, ensuring an easy transition from me as the Acting Editor and **Salil Desai**, PhD, as the Assistant Editor to him and **Mia Ricci**, the new Assistant Editor. Mia brings several years of scientific journal experience to the role, having worked as an editor for John Wiley & Sons, Inc. Special recognition goes to Salil, who worked for former Journal Editor **Lee Kirsch** and graciously stayed on to help us during the period of transition. Salil continued doing most of the logistics for the Journal—managing submissions from review to production, communication with authors, etc.—all while completing and defending his dissertation and earning his PhD from the University of Iowa. We wish Salil all the best as he moves into his new post-doctorate career and anticipate a long and productive relationship with Govind and Mia.

Joining Govind and Mia on the editorial team are three well-qualified Associate Editors, all very familiar with PDA: **Kurt Brorson**, PhD, U.S. FDA; **Anurag Rathore**, PhD, Indian Institute of Technology (formerly with Amgen); and **Antonio Moreira**, PhD, University of Maryland Baltimore County. Continuing the Journal's presence in Asia through affiliating with Anurag is important, and we believe it will be equally important to strengthen connections in Europe with possibly the addition of an associate editor from there, too. The backgrounds of these editors also demonstrates our commitment to ensuring the Journal provides valuable content to not just the traditional small-molecule side of the industry, but also to the biopharmaceutical side.

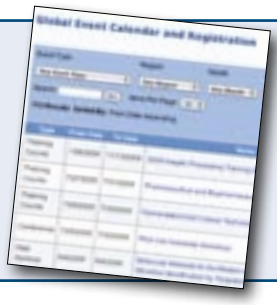
By the time you read this, notifications about the new Journal website at http://journal.pda.org will have been sent and you will have had time to explore the new site, which includes articles going back through the 1998 volume year. We are eager for feedback because moving so many issues over to a new online format was a large and costly project for PDA, and we don't anticipate all the bugs to be ironed out of the new website for a month or two. So the more feedback we receive, the better! Members will find the various features of the website—searching, M.S. Powerpoint downloads, RSS feeds, archives—extremely useful.

We launched the site with the July/August Journal, a special issue in which every article addresses topics related to extractables and leachables. The "Journal Preview" on the next page has more on this issue. It is worth noting that July/August is the last issue I helped prepare as Acting Editor, and I am proud to have spent a great deal of time working with Salil and the various authors on it. I think the members will find the edition very informative. We hope for more themed Journals in the future.

We anticipate posting the first edition under Govind's care early in September, so be sure to log in at the new website and sign up for the e-TOC notification.

Last month, we declared a new era was underway for the Journal, and so far, it has been a great start. Once again, please send us your feedback. The new Journal editors can be reached at journal@pda.org. General questions about PDA publications can be directed to me at levy@pda.org, or Publications Director Walter Morris at morris@pda.org.

To learn more about upcoming meetings, conferences, workshops and training events, go to www.pda.org/calendar.



Journal *Preview*

A Look at Extractable and Leachables

The July/August issue of the PDA Journal is a special one focused on extractables and leachables, a very important issue for biologics and other kinds of sterile products, particularly with the increasing use of disposable manufacturing components and the number of novel delivery systems in use. Articles in the issue look at various packaging types.

Be sure to go to http://journal.pda.org to access this issue and all the 2009 and 2008 issues for free!

Commentary

- Alda Laschi, Natacha Sehnal, Antoine Alarcon, Beatrice Barcelo, François Caire-Maurisier, Myriam Delaire, Marc Feuilloley, Stéphanie Genot, Catherine Lacaze, Luc Pisarik, and Christophe Smati, "Container–Content Compatibility Studies: A Pharmaceutical Team's Integrated Approach"

Research

- Dennis Jenke, Tom Couch, Amy Gillum, and Salma Sadain, "Modeling of the Solution Interaction Properties of Plastic Materials Used in Pharmaceutical Product Container Systems"
- Daniel L. Norwood, James O. Mullis, Thomas N. Feinberg, and Letha K. Davis, "N-nitrosamines as "Special Case" Leachables in a Metered Dose Inhaler Drug Product"
- Weibing Ding and Rebecca Nash, "Extractables from Integrated Single-Use Systems in BioPharmaceutical Manufacturing. Part I. Study on Components (Pall Kleenpak™ Connector and Kleenpak Filter Capsule)"

Technology/Application

- Daniel J. Zuccarello, Michael P. Murphy, Richard F. Meyer, and Paul A. Winslow, "A Comprehensive Approach for the Determination of Extractable and Leachable Metals in Pharmaceutical Products by Inductively-Coupled Plasma"
- Cindy Zweiben and Arthur J. Shaw, "Use of Thermal Desorption GC-MS to Characterize Packaging Materials for Potential Extractables"
- Frances Degrazio, Joseph Runkle, Jeff Smythe, and Amy Miller, "Analysis of Biopharmaceutical Market-Appropriate Plastic Syringe Barrel for Extractables"

In *Print*

Aseptic Processing Innovations

The following is excerpted from the chapter, "Innovation In Aseptic Processing—Case Study Through the Development of a New Technology," by Benoît Verjans and Jacques Thilly, Aseptic Technologies. The chapter appears in the recently published PDA/DHI book, Practical Aseptic Processing: Fill and Finish, Volume II, *edited by Jack Lysfjord. References have been removed for this excerpt, but can be found in the book.*

In 2002, Aseptic Technologies, a subsidiary of GSK Biologicals, started to investigate the opportunity of using a new technology for aseptic filling of injectable drugs. The reason for this search was based on several drivers with four major ones.

First, the overall injectable industry is concerned about the quality of aseptic filling as several accidents were reported worldwide. Effectively, despite a lot of care provided to aseptic filling operations by pharmaceutical manufacturers and authorities, the risk is always present. Some examples hereby illustrate the risk of contamination:

- A recent example happened in Brazil in a period of one month, 28 newborn babies died in a single 200-bed hospital (CDC, 1998). After investigation by the Center for Disease Control and Prevention, it appeared that a Brazilian pharmaceutical manufacturer produced batches of contaminated injectable drugs due to process issues.
- Contamination of a needle when the stopper surface is not properly treated by the healthcare practitioner is another common issue, often less dramatic, but which can trigger severe contaminations.
- In a recent market study (conducted by an independent agency on request of Aseptic Technologies), 246 healthcare professionals were interviewed in both Europe and the United States. Among the questions, they were asked to comment on their experience with contaminated vials. Astonishingly, 4% in Europe (5/136) and 8% in the United States (9/110) declared that they have already seen a contaminated vial.

Second, a new concern on injectable products appeared as different agencies have jointly recommended to withdraw preservatives from drugs to be injected to children and to pregnant women. Preservatives, such as Thimerosal, are bacteriostatic and fungistatic agents, which then act as the last safety barrier in case of contamination (CDC, 1999).

Third, a new threat, already present in the third world countries, has started to surface in developed countries:

continued on next page

Aseptic Processing Innovations, continued from previous page

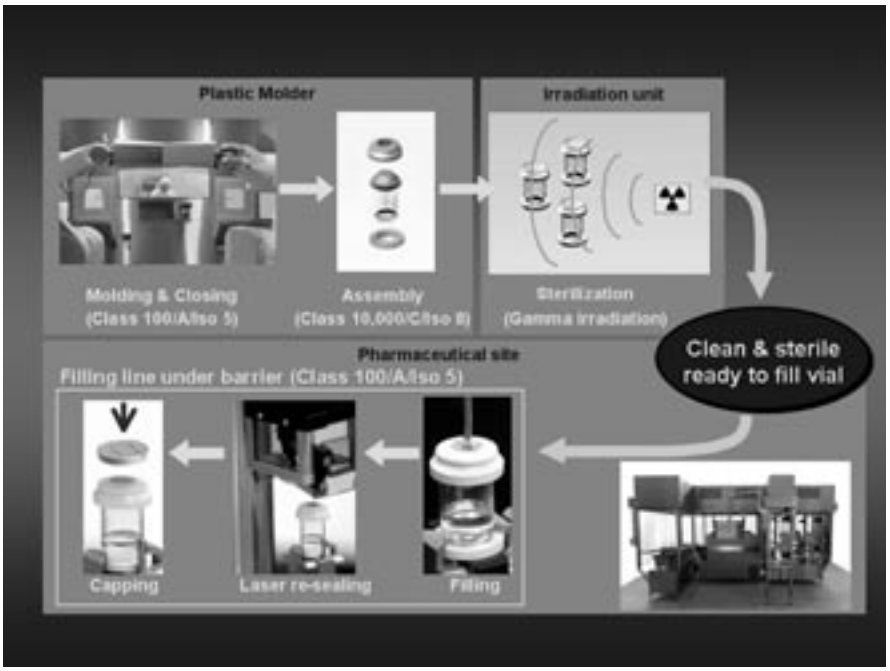
counterfeiting. Counterfeiting is a major issue from various points of view:

- Economic point of view—it is estimated that about 10% of worldwide drugs are counterfeited, generating a revenue loss of more than 32 billion USD. Counterfeiting is so severe that it can reach up to 50% of drugs sold in some countries such as Nigeria (WHO, 2003).
- Patient quality point of view—the quality of counterfeited drugs is seriously impaired. In some cases, the active ingredient is not present or not at the right dosage leading to the lack of treatment and worsening of condition. In the most serious cases, the drug is contaminated and lead to serious side-effects. The most well-known case is the contamination of Tim Fagan, a teenager with a recent transplant who has been contaminated by a poor quality copy of Amgen's drug Epogen. This case brought to general knowledge that an undermining threat has started to hit the United States. As a result, a law, named Tim Fagan's Law, has been approved and has reinforced legal actions against counterfeiting companies and people.

The major problem with current glass vials is that they are very simple to copy as they are easy to produce and are present everywhere in the world.

The fourth driver was based on the experience of the Aseptic Technologies founders on glass vial filling in an isolator. The equipment used has reached such a level of complexity that each produced batch requires high levels of resources both in qualified personnel for operation and maintenance, but also in QA/QC support. The complexity is mainly driven by the washing, siliconization and sterilization of vials and stoppers, the high speed filling/stoppering and the high speed aluminum capping. As a result, both operating expenses and investment for equipment, large utility production units and building space have exploded. For example, a filling line under isolator with a nominal capacity of 42,000 vials/hour needs approximately 300 m2 of class C (or class ISO 8) clean room and overall equipment price would exceed 10 Mio EUR.

Figure 30.1 Overview of the closed vial technology process, including vial manufacturing, vial sterilization and vial filling



As an outcome of these constraints, Aseptic Technologies investigated the possibility of creating a new technology which would be able to address all these issues together. This means that the technology should:

- Provide a top-class sterility assurance level during operation
- Provide a reinforced security against counterfeiting and bioterrorism
- Simplify aseptic filling processes and operations

The Closed Vial Concept

To address the three expectations detailed here, the aseptic filling process was completely put in question and rethought from a blank page. The outcome was to develop from a concept based on a closed container, which can be filled through a heat re-sealable stopper (Core technology licensed from Medinstill Inc.), and to industrialize this concept for all injectable drugs to be aseptically filled, such as vaccines, antibodies, proteins and all other heat-sensitive products.

The major implications of such a process would be:

- The stoppered vial needs to be delivered clean, sterile and pyrogen-free, as it will not be washable on vial filling line
- The filling process requires a specific needle able to dispense the liquid through the stopper without creating significant particle generation and/or overpressure inside the vial
- A well-controlled source of heat should be delivered specifically to the stopper part which needs to be re-sealed without affecting the product.

To answer to the three implications, crystal technology has been developed. It consists in six major steps in the vial manufacturing and filling processes as illustrated in Figure 30.1.

First, the vial is produced in class 100/ISO 5 to ensure the cleanness of the inside of the vial. The manufacturing consists in molding both the vial body and the stopper at the same time, and then robotically picking them up and immediately assembling them together. By this

means, the air entrapped inside the vial is from class 100/ISO 5 environment. Molding in a clean room requires a material which does not generate particles and which can be further processed without a washing step. Therefore a plastic with excellent characteristics for pharmaceutical container has been selected: cyclo-olefin copolymer (COC).

The second step consists in securing the closure integrity by adding top and bottom rings. In particular, the top ring is of a right angle snap fit structure which fully secure the closure integrity with a simple pressure assembly.

The third step is the sterilization of the closed vial. As there is no glass, gamma-irradiation is appropriate to ensure that the vial is sterile.

These three steps allow the generation of a clean and sterile vial which is ready-to-fill once delivered to the pharmaceutical manufacturing site.

The last three steps consist in vial filling, laser re-sealing and capping. Prior to performing them inside a barrier, the stopper surface is irradiated again with a mini e-beam to ensure that any accidental contamination of this critical surface during vial loading is eliminated.

The filling of the vial is made in a class 100/ISO 5 barrier. First a pencil point needle pierces the stopper to dispense the liquid, followed by a laser re-sealing which will melt the stopper and restore the closure integrity once cooled down. To that end, it was critical to use a material able to absorb the laser energy, melt and fuse to restore the closure integrity. The classical rubber stopper would have burned if laser energy was sent to it, but the piercing trace would never be closed. Therefore, a thermoplastic elastomer or TPE material has been selected for the stopper.

The last step consists of capping the vial with a plastic cap using a snap-fit principle. This cap has the property of protecting the piercing area and keeping it in same conditions as the class 100/ISO 5 manufacturing environment until use by the healthcare professional.

Recent Sci-Tech Discussions: Reporting Injectable Content, Injection Particulate Matter Testing

The following unedited remarks are taken from PDA's Pharmaceutical Sci-Tech Discussion Group, an online forum for exchanging practical, and sometimes theoretical, ideas within the context of some of the most challenging issues confronting the pharmaceutical industry. The responses in the Sci-Tech Discussions do not represent the official views of PDA, PDA's Board of Directors or PDA members. Join at www.pharmweb.net/pwmirror/pwq/pharmwebq2.html.

Reporting Injectable Content

How do you report the content as a percentage of a label claim when extra amounts are added? E.g., with sterile injections, 10ml needs 5% extra to compensate for the amount not usable. When a sample is tested for content, it will show 105% in the vial. Should that be 105% (compared to the label on the product) or 100% (compared to the expected assay)? The problem is that it can easily be over 105% and pass the upper limit.

Respondent 1: Dear [Questioner],

For sterile injections, the content is typically defined as a "not less than (NLT)" limit. For example, the spec would say "NLT 10 ml per container." The caregiver should be easily able to withdraw at least 10 ml from the container, but inject exactly 10 ml into the patient (if that is what your product insert claims).

Questioner 1: Thanks [Respondent 1], and I think you are right on that point of view.

However, if the product needs to be between 95-105% of label claim, and if the QC lab finds 106% because of the extra amount added, what would be the way out? If the product should contain 105% (because of extra 5% added), should the QC limits be 105 +/- (tolerance)%?

Respondent 2: In the European Union there is legislation that requires a target of 100% fill for many containers with a permitted scale to allow for deviations in the fill volume.

The Pharmacopoeia requires not less than the stated amount, but then any excess volume should not present a hazard to patients should the total volume be administered. This is likely to be most critical for injection products. In practice, it is acknowledged that a small overfill is required to ensure normal withdrawal of the dose from the container.

Special provisions may apply to controlled drugs (e.g., morphine) where accountability for every milligram of active will be required.

Respondent 3: It is not clear from your message whether the 5% extra is simply an extra .5 ml of product, or whether the concentration (mg/ml) is targeted at 105% of the claim. If the former, the assay should come out close to 100% on a mg/ml basis. No problem. If you are doing the latter, I would ask why.

Respondent 3: "In the European Union there is legislation that requires a target of 100% fill for many containers with a permitted scale to allow for deviations in the fill volume.

"The Pharmacopoeia requires not less than the stated amount, but then any excess volume should not present a hazard to patients should the total volume be administered. This is likely to be most critical for injection products. In practice, it is acknowledged that a small overfill is required to ensure normal withdrawal of the dose from the container.

"Special provisions may apply to controlled drugs (e.g., morphine) where accountability for every milligram of active will be required."

But is this a case of overfill? Overfill should not give an assay of 105%.

Respondent 2: By "overfill" I assumed that the quantity of the product was increased, not its concentration. Changing the concentration changes the product. The assay should therefore be based on 100% of nominal value—unless a stability overage is included.

Respondent 4: [Questioner],

From what I understand, the 5% extra added is in terms of volume, so you have a "real volume" of 10.5 ml, instead of 10 ml, correct? I'm not sure if I'm missing something in your query, but when you test for "content" (as you mention in your e-mail), you basically have to express the result in mg/ml, and this is independent of your final volume.

If, for some reason, you need to express your potency as total quantity-per-vial (for instance 200 mg), you do not have to take into consideration the "excess" of volume in the vial. You only have to use the "nominal" volume (i.e., 10 ml).

Hope this helps!

Questioner: Thanks for all comments. I will add more details to make it clearer. Product has 2mg/ml and vial has 10ml. Total in vial is 20mg. To make sure the user can take 10ml, 10.5ml is added to vial so that the user can take 10ml accurately.

Because of 10.5ml, now the total content in the vial is 21mg. But the concentration is still 2mg/ml.

QC testing is done by transferring the total content into a flask followed by rinsing the vial into the same flask. QC results will show that there are 21mg of content in the vial. The label claim is for 20mg per vial. Is the result 105% compared to the label claim?

Respondent 2: [Questioner],

I would have thought that it is more common to (a) measure the total volume in the container e.g., by transfer to a graduated cylinder or by weight difference (full and empty), and (b) assay the contents (mg per ml).

The target fill volume should include the excess volume to allow dose withdrawal.

Unless you are working with materials such as controlled drugs (e.g., morphine), it would not usually be necessary to calculate the total weight of the drug in the container in the case of a liquid product.

Respondent 5: Dear [Questioner],

The procedure for QC testing is incorrect. They should take some of the measured volume. Because your final claim will be based on per ml not per vial.

Respondent 6: [Questioner],

I suggest each time you remove the sample solution from a vial or ampoule, use a micro syringe or a well calibrated micropippette to withdraw the exact volume you need followed by cleaning the exterior surfaces of the tips. The accuracy of such sampling is within 1% error of 1 ml samples. I am not sure emptying the container or flushing the content out of it with a diluent is a good way of assaying your drug content in each one of the test units. Not only will you have overage >100% recovered, you also have a large variation from sample to sample.

Respondent 7: [Questioner],

The total per vial is still 20 mg. The labeled volume is still 10 ml. The extra is to ensure that the patient receives the 10 ml. The extra volume does enter into the calculation, but it is only part of the deliverable volume requirement. The EMEA regulation specifies volume based on volume delivered to patient. The United States requirement is based on volume removed from the container. They are not exactly the same. The European regulation takes the hang up in the vial plus needle volume into consideration, and the United States only considers hang up in the vial.

The label claim is based on delivery to patient. The only time you would consider the extra is for lyophilization and dry powder so when diluent is added the correct final concentration is achieved.

Respondent 1: [Questioner],

The excess fill to compensate for the withdrawable volume does not factor into your calculation for +/- 5% at all, as the label claim is based off the "target withdrawable" volume (10 ml) and does not include the excess fill (say, 0.5 ml).

Respondent 8: [Questioner],

Can you confirm the label claim?

Questioner: [Respondent 8],

Label claims are 20mg per vial and 2mg per ml.

Now I am not sure whether we can say 20mg per vial if we add an extra 5% into the vial. But still the 2mg/ml is valid. Maybe the label claim should only be 2mg/vial and we should calculate the results per ml and report it as a percentage of label claim.

Respondent 2: [Questioner],

The expression of content of a vial is in some cases controlled by local legislation. It is reasonable to assume that it is the usable extractable volume that is labeled.

Injection Particulate Matter Testing

With particulate matter testing in injections (SVI), is a visual inspection not sufficient? Must a light obscuration particle count test be done? Could you give some comments please?

Respondent 1: There are two separate requirements: (1) absence of visible particulate matter—these apply to all injectables, and (2) controls on subvisible particulate matter using instrumental methods of detection (which is required in relevant cases). The definition of "relevant" will depend on the pharmacopoeia being worked to and will possibly depend on specific requirements required by the local regulatory agency.

Respondent 2: Filled containers of parenteral products should be inspected individually for the presence of particulates and other defects. When the inspection is done visually, it should take place under suitable and controlled conditions of illumination, background and line speed. Every container whose contents shows evidence of visible particulates should be rejected. Qualified operators doing the inspection should pass regular eyesight checks and should be allowed frequent breaks from inspection. Qualified operators should be subjected to routine checks for their efficiency in detecting defective units. Where the other method of inspections are used, e.g., mechanical inspection, the process should be validated and the performance of the equipment should be checked at appropriate intervals.

I am providing some references for further reading.

Regulatory Guideline References:

1. "FDA's position on Visual Inspections: Particulate Matter and Glass, Albinus D'Sa, Office of Compliance, CDER, U.S. FDA
2. "Visual Inspection: the British Pharmacopoeia's Perspective" Stephen Young, MHRA, Berlin, October 14, 2008
3. PIC/S GMP Guide - PE009-8, *Annex 1 - Manufacture of Sterile Medicinal Products,* Point No. 124.
4. Health Canada, *Good Manufacturing Practices (GMP) Guidelines*, 2007 Edition, Draft for comments, Point No. 84, Page 93.
5. Health Canada, *Good Manufacturing Practices (GMP) Guidelines*, 2002 Edition, Point No. 20, Page 76.
6. *Guide to Inspections of Dosage Form Drug Manufacturer's -CGMPR'S,* Office of Regulatory Affairs, U.S. FDA
7. WHO TRS 902, Annex 6, *Good Manufacturing Practices for Sterile Pharmaceutical Products*, Point No. 11.3

Compendial References:

1. "USP Parenteral Products - Industry Expert Committee, Work Plan for

continued on page 15

PDA Interest Groups & Leaders

PDA Interest Groups are divided into five sections by subject matter. This aligns them for improved effectiveness, supports increased synergies and provides the opportunity for Interest Group members to play a more active role in Task Forces. The five sections are Quality Systems and Regulatory Affairs, Laboratory and Microbiological Sciences, Pharmaceutical Development, Biotechnological Sciences and Manufacturing Sciences. PDA's goal is for each group to have co-leaders from the three major regions in which the Association is active: Asia, Europe and North America. Any PDA member can join one or more Interest Group by updating their member profile (www.pda.org/volunteer). Please go to www.pda.org/interestgroups for more information.

SECTION TITLE

Biopharmaceutical Sciences	Laboratory and Microbiological Sciences	Manufacturing Sciences	Pharmaceutical Development	Quality Systems and Regulatory Affairs

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Recent Sci-Tech Discussions, continued from page 13

2005-2010, Revision Cycle," Scott Aldrich, USP

2. European Pharmacopoeia 5.0, 2.9.20. *Particulate Contamination: Visible Particles*
3. British Pharmacopoeia 2009, Volume III, General Monograph on *Parenteral Preparations*
4. USP 32, <1> General Requirements for Injections, *Foreign and Particulate Matter*
5. USP 32, <788> *Particulate Matter in Injection*
6. International Pharmacopoeia, 3rd Edition, Volume 4, *Tests, Methods, and General Requirements: Quality Specifications for Pharmaceutical Substances, Excipients, and Dosage Forms*
7. Japanese Pharmacopoeia, 15th Edition,<11> *General Rules for Preparations: Injections.*
8. Japanese Pharmacopoeia, 15th Edition, 6.06, *Foreign Insoluble Matter Test for Injections*
9. Japanese Pharmacopoeia,15th Edition, 6.07, *Insoluble Particulate Matter Test for Injections*

Respondent 3: [Questioner],

Others have given good answers to what has to be done. I just want you to understand why the visible size cut-off is 50 microns. The subvisible sizes that are tested (specs) refer to 10 and 25 microns. So you see that they are in fact two different tests with different criteria.

Respondent 4: [Questioner]:

I believe that if you did a risk-based analysis you'd find that visual inspection of small volume parenterals (even with 100% inspection) is not effective in weeding out all the particle containing ampules. It does take light obscuration testing or better still, automated, single amp conveyor belt light testing for total surety.

Respondent 5: Parenteral products in all volumes must comply with particulate matter determinations by visual inspection and subvisible method analyses according to USP, EP and JP compendia, as well as many others. Since visual inspection detects the obvious and visible material down to about 150 micrometers, the subvisible assays detect those and others below this size threshold. Both parenteral products and ophthalmic solutions must be tested in this manner for USP compliance.

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ICH Q7: A Worldwide Guide, continued from cover

around the world. PIC/S [Pharmaceutical Inspection Cooperation Scheme] also adopted Q7. Over time, I've seen the document translated into Spanish and other languages by regulatory authorities in Latin America. It is used by other regulators around the world. This is an improved situation for the industry, because again, we don't have a variance in the expectations; everybody is working off of the ICH Q7.

GM: And in some ways we actually reduced the expectations, because in the absence of an internationally agreed upon standard there were people doing, for example, controls on early stages of manufacture, which were inappropriate for an API. Because of the nature of the chemical process, as you proceed through the synthesis, you can and do purify the material as you go along so you don't need such stringent controls during manufacture as you would do in manufacturing a finished product. But there comes a point when you cannot and don't achieve further purification, and so what we did was to establish where we believed that point was and enforce a proportionately stronger GMP after that. So that is an example of how we reduced some of the burdens on the industry while improving the consistency to the quality of the product that comes through to the patient.

Equally importantly, it produced a level playing field, because Q7 was not only adopted within the ICH arena—the United States, the European Union and Japan—but it was also picked up by PIC/S as their GMP, and that now involves about 35 countries around the world. Other countries such as India and China seem to recognize it officially or unofficially as the global standard, so for the industry there is a level playing field.

PL: So what was it like before Q7? What was going on prior?

GM: There were a range of API standards around the world either in place or being developed. There was a WHO [World Health Organization] one, the U.S. FDA had standards, the industry association in Europe was producing one—CEFIC [European Chemical Industry Council], which is part of EFPIA [European Federation of Pharmaceutical Industries and Associations]—the PIC/S was producing an API standard, and there were other countries also developing their own. In addition, many big companies developed their own in-house standards. So there was a range of standards around. What we did with Q7 was to bring together a group of international experts and take into account all the standards that we knew of and then develop what we thought was a best practice document.

Until Q7, what you had to do to attain compliance often depended on which market you were selling to as there were differences in requirements not necessarily big, but still potentially leading to reduced efficiency and effectiveness and variability of quality.

PL: Does FDA benefit from Q7? Other regulatory bodies?

ERM: Yes. One of the major benefits made possible by Q7 is the API Pilot Program between the United States, EMEA and TGA, which provides for sharing of information about API inspections between regulators and conducting joint inspections, in some instances.

The only way this is really possible, Walt, is because we have Q7 today. If we didn't have Q7, it would be very hard to go out and do this type of cooperation between three regulators. Without Q7, you can imagine how difficult this would be, because we would be inspecting to different standards.

GM: I think there are a number of benefits. I think the first one is regulators having a common standard and a common application of that standard. When we got Q7 agreed and accepted, a number of the members of the Q7 working group created a significant training package which we delivered in the United States and in Europe. PDA was very

heavily involved with that. The idea was pretty unprecedented at the time. What that did was to really roll Q7 out and put in place not only a common standard, but also a common understanding and interpretation of the standard, which was tremendously important. For regulators, it means they are truly working to the same standard. So even if you don't have a Mutual Recognition Agreement or some kind of Memorandum of Understanding, if you know an inspectorate from another country has gone to a manufacturing site for APIs in a third country and you can be reasonably sure that the inspectorate that went conducted a thorough inspection working to the ICH standard, while they may not officially be able to say they can accept that inspection report, they are certainly more likely to take it into account, for example, in determining the frequency of inspection.

PL: So Q7 makes it possible, and it gives the FDA, TGA and EMEA assurance that you understand exactly what the other investigators are going to be looking at.

ERM: That is correct. We have a standard. Q7 defines the expectations, and the API manufacturer that is being inspected clearly knows what the expectations are on the part of the regulator.

It is a win-win situation for everybody involved—for the regulators, for the

industry and eventually for the consumer. With Q7 we have one GMP expectation for APIs. We cannot really say that for any other type of manufacturing process in the pharmaceutical industry. Having one GMP document for APIs has really been to FDA's benefit, to all the other regulators' benefit and overall to the industry, because, I think, the industry really appreciates the fact that they don't have to deal with different GMP regulations or guidances. Every time a different inspector comes in they don't have to look for the regulation or guidance that applies.

GM: The API pilot which Edwin mentioned is a very good example. But unofficially, I think a lot of other countries do the same thing. I know within PIC/S they adopted the Q7 GMP, so you have some about 35 countries there—well, the European Union countries already exchanged and accepted their inspection reports, because that is part of EU Legislation—but the non-European Union members of PIC/S used Q7 and exchange reports based on it.

PL: Q7 wasn't really a document that changed what firms were doing. You mentioned the documents under development at the time. In retrospect, is this true, and, if so, is it time for a revision?

ERM: From my perspective, I feel it was relatively easy for most API manufacturers to adopt and comply with Q7, because in my opinion, Q7 was simply a compilation, a summary of what the FDA and perhaps other regulators were already requiring or expecting from API manufacturers. The only exception that I can recall is the language on impurity profiles and the chapter dealing with agents, brokers, distributors, repackers and relabellers.

Again, Q7 did not represent a large paradigm shift to the API industry, whether we are talking about innovator companies manufacturing their own APIs or companies producing APIs for generic companies.

GM: I think we did capture best practices. I have to say, we had a very strong team. We had some excellent people in there who really worked together as a team. They were drawn from the API industry, big pharma and generic pharma. We had a couple of people from the over-the-counter areas. We had somebody from herbals. We had people from Japan, America, Europe and the World Health Organization. We had input from people from India and China from time-to-time—not necessarily the same people. They didn't have a vote, but we kept them aware of what was developing. So yes, we worked very hard to get best practices and keep it simple. I think that is the other good thing about Q7, it is essentially a pretty simple document to follow.

Is it relevant today? I think it is every bit as relevant as when it was first created. I think it is still useful and I know it is widely used across the industry. Is it reaching a point where it might be necessary to revise Q7. I'd use the word, 'review' rather than 'revise.' I think any

document that has been around for nearly 10 years is probably getting to a stage where it would be worth reviewing and then deciding whether there were some areas that would need revision.

ERM: I agree with Gordon. Q7 is still relevant and useful today. While it is still an excellent document, there are a few areas that would benefit from further clarification. These include clarifying the importance of proper GMP for starting materials, the importance of at least partial impurity profiles for natural materials and addressing supply chain issues. These three areas certainly are of great concern to everyone and have some ambiguities of interpretation that could be resolved by some additional clarification.

PL: Do you see changes in the industry and the supply chain with Q7 in place?

GM: Step back a little bit, I think the supply chain in terms of sources of raw materials for APIs, the supply chain for APIs themselves coming into Europe, the United States and Japan is basically the same as it was 7-8 years ago. However, I think the amount of material that is now coming from developing countries has increased and the amount of materials manufactured in Europe, the United States and Japan is considerably less. So though the supply chain to me is essentially the same, we are seeing far more materials being manufactured outside of the ICH areas. What that has done is mean that there has been less direct control by way of inspection and review by the countries where the majority of those APIs are sold in finished products. When the API gets to the patient in a larger proportion of the time, the API is coming from a developing country where it, until recently, has been subjected to less frequent inspections and arguably less rigorous control then when it was manufactured in America, Europe or Japan. That is a significant change, and that has led to a lot of the pressure, for example, which has been put on FDA to bring their frequency of inspection and duration of inspection in developing countries up to the same levels that they would do in the United States, the European authorities would do in Europe or the Japanese authorities would do in Japan.

The Expert Working Group was trying to include some responsibility for all of these other entities that may handle the API after the material has left the manufacturing site

Behind that, I'll come back to Q7, the key thing is having a common standard for these people in developing countries. New companies coming into API manufacture, old companies wanting to meet western standards—the ICH standards—they need to have an easy to understand document that sets out the right guidance for API manufacture, and they have that in Q7. That is facilitating that change in the supply chain.

PL: It seemed like an easy transition/implementation, but there was the whole section on the traceability. It introduced the need for the various entities in the supply chain to meet, possibly, new expectations. Has that chapter had an influence on the changing marketplace?

GM: I think it has. Interestingly, while we were developing Q7, I had a number of meetings with a number of brokers, distributors and repackager associations. They were actually very keen to input to and comply with Q7, as it applied to them. They weren't really at the table, but they certainly sent us quite a lot of information and quite a lot of their thoughts on how best to control it. With the legal side of the supply chain, firms like that have tried to make sure they comply with those types of requirements, which helps us end users of APIs. And yes, the need for identification of the source and traceability, I think, as has been emphasized recently with a number of the horror stories that have been around, that is absolutely essential.

ERM: Yes, that whole chapter dealing with brokers, traders, distributors and everything else under the sun was written because of the Haitian incident involving contamination of glycerin with diethylene glycol [DEG]. The Expert Working Group [EWG] was trying to include some responsibility—expectations—for all of these other entities that may handle the API after the material has left the manufacturing site.

Our concern was heightened by what had happened in Haiti. In this case, if you recall, it was glycerin that was supposedly manufactured by a Chinese company, and it went to a distributor in the Netherlands. Then from there it went directly to the Haitian pharmaceutical manufacturer that manufactured the pediatric cough syrup. And of course, there was not only the issue of the supply chain integrity and traceability, but also there was serious lack of GMPs along the way. Every time the material exchanged hands in the distribution chain, there was no testing of the material. Everyone basically took the information on the certificate of analysis [COA] and transposed that information onto their own letterhead. We later learned that the distributor tested the material before they sent it to Haiti. They noticed an unknown peak, but they never identified the peak and never notified the consignee of this unknown peak in the glycerin.

This chapter in Q7 was written to impose some responsibilities on these other entities—they have a responsibility to provide high-quality materials uncontaminated to their consignees, and they need to do whatever is necessary to provide this assurance.

PL: It is up to the firms to keep track of all of this? And do firms like Watson have trouble getting it?

GM: No significant problems of which I am aware. More and more,

companies have quality agreements, in place and that is where we spell out our terms and conditions of purchase—the kind of requirements that have to be met—and for APIs that is largely based on Q7.

ERM: Essentially. The ultimate responsibility, or most of the responsibility, falls on the ultimate user of the material. That is a concept that has not changed over the years. It is even a concept that is in 21 CFR 211. The ultimate user of any raw material/pharmaceutical ingredient has the ultimate responsibility to assure the quality and safety of that material before they use it in a drug formulation.

PL: Now we move forward to the continuing problems in the supply chain, in spite of Q7. The whole interview, Gordon, has emphasized the legal market, but there is an illegal market that exists. What more can be done by industry and regulators about this?

ERM: One of the things that I think is relatively different nowadays is the involvement of criminal elements in the supply chain. Companies or criminals find it is relatively easy to substitute or counterfeit a pharmaceutical ingredient or drug product, and they can make a lot of money out of it. If they get caught, the penalties today in most countries are probably pretty insignificant. The punishment does not fit the crime, essentially, particularly if they kill people in these acts.

Economically motivated adulteration is a growing concern, as evidenced by recent well-publicized contamination and counterfeiting situations—the whole situation with melamine and pet food and milk in China, the heparin contamination and several DEG contamination incidents in Panama, Nigeria and Bangladesh.

This is a situation that is very, very difficult to deal with. It is going to take all kinds of different approaches to try to deal with this problem. We are currently exploring options within the Agency and talking to other regulatory bodies, to traditional law enforcement agencies, and to the regulated industry.

GM: If those of us in industry knew all the answers, we wouldn't be having these incidents. A number of things come to mind, and one of them is around intelligence gathering. If you take the heparin incident, and you are being wise with hindsight, you could see a supply shortage situation arising where China was the largest source of raw materials—pig intestines—and there was an epidemic amongst the pigs (blue ear disease). It is a big export market to them and when it looked like demand could not be met, it opened up an opportunity to the criminal fraternity to do something to meet the shortfall in demand. So off they went and did something criminal. As it happens, it was very, very difficult to detect. So a lot of people probably made a lot of money and a lot of people here got defective medicine.

Economically motivated adulteration is a growing concern, as evidenced by well-publicized contamination and counterfeiting situations

PL: Who should do this intelligence gathering? Is it more the responsibility of the companies?

GM: I think, like a lot of things, it's got to be a shared responsibility at various stages. I think companies in their own best interest need to be looking for these kinds of situations, and need to have good knowledge of their own supply chain—where the materials come from, where the raw materials for APIs or excipients come from—and just keep a watchful eye in general. But we use so many materials, it is always possible for some of this stuff to slip beneath the radar So I think it would also be useful if the regulators around the world were sharing more of this type of information. The other thing that I think needs to be done, and I think the regulators have a major role to play, is when these things happen and there are criminal acts they are fully investigated, prosecuted and that there are appropriate penalties in place proportionate to the crime. In quite a number of countries, the penalties right now are totally inappropriate, in my view.

We also need to encourage the people on the ground in the countries where these products are manufactured to take stiffer action, because it can be difficult to extradite the criminals. At the end of the day, it is every much in those countries' interests, wherever they are manufactured, to deal with this type of problem.

PL: So has the FDA and EMEA and the other authorities agreed the solution to this will have to be harmonized?

ERM: We all recognize that we need a unified approach or solution. It is going to require the cooperation of drug regulatory bodies and traditional law enforcement agencies around the world. It is going to require the cooperation of industry. The topic has been discussed extensively at the PDA/FDA Supply Chain Integrity conferences and other industry forums, but we need to work closely together in order to find solutions.

PL: It is worth noting that Q7 is not discussed at these conferences.

ERM: You are absolutely right. Q7 is not discussed at these conferences, but there is some language in the guidance to deal with the issue of, for example, certificates of analysis. I think Q7 was one of the only documents at the time that discussed authentic COAs. We said companies need to get an authentic certificate of analysis and should not accept this information by fax or any other means. They should actually ask for the COA on an official letterhead; an original document with an original signature and contact information. We

spelled out what an authentic certificate of analysis was.

When we were writing Q7, the Expert Working Group understood that it was common practice for companies to transpose information from one certificate of analysis to another and not retest the API. This is a problem that continues today. It has been recognized by the International Pharmaceutical Excipients Council. They have developed and issued a more detailed guidance on certificates of analysis and how to deal with this problem—what to expect in terms of COAs.

PL: This has been a great discussion. Just to conclude here, what strikes me as we've been talking, Q7 still stands out as a unique ICH, in the respect that, one, it created new regulatory expectations where they didn't exist prior, and two, it stands out as the only GMP in the quality side of ICH so far. Is Q7 a model for future ICH work? Are the new Q's, 8-11, following in Q7's footsteps?

ERM: No, those documents are different. Like you said, Q7 stands out as the only GMP document in the ICH. It has been a very successful document. I can say that most if not all regulators are using Q7. Some may not have adopted it yet or may be in the process of doing so. But I think most of the industry around the world has looked at Q7, and are trying to comply with it. And that in itself is a significant achievement.

It was unique when the EWG first wrote it. We didn't know what we were really getting into. We didn't realize the impact it would have afterwards. All of the expert working members were dedicated professionals. We really discussed the

issues. Some of those discussions were very long and complicated.

I think we wound up with a document that was very novel for its time. Q7 is a risk-based document although we were not talking about risk-based approaches at the time. But if you look at it, the way it is written, it is actually a risk-based document. It talks about critical processes, critical process controls, critical deviations, and it defines critical. It places a lot of emphasis on critical operations and processes, and less control over noncritical process. I think that in itself it represents a risk-based approach.

When writing Q7, we did not want to write another 211. We wanted to write a document that actually recognized the uniqueness of API manufacturing and reflects the practices of the API industry. Keeping that in mind, we were quite successful. So successful that some people wonder why we have certain language in Q7 that deviates from 211. I can give you an example. 211 does not allow for production personnel to sign off on a batch record to allow continuation of a process. It has to be somebody from quality. But, this is permissible in Q7 in certain circumstances, particularly when you are dealing with an in situ intermediate, which means the intermediate is not actually isolated. The EWG extensively discussed if it is really necessary for the quality person to come down and review the batch records, and give it the green light before the next step can be initiated. And we agreed it is not necessary. A qualified production person or supervisor can review the batch records up to that point and okay that manufacturing process. This is something unheard of in the 211 world. There was a lot of consternation about it, but we said, 'what's the risk? We are dealing with APIs here.'

GM: Absolutely. It was. In all of our discussions around what was the best practice, we inevitability had a risk element in the conversation.

I remember when we were talking about most things, we'd go back to 'what's the risk?' And that was how we set up the whole concept of the "API Starting Material" as the definitive point of the start of the later stage of synthesis, which had to be controlled more fully. We believed that the risk during synthesis until you got to that API starting material, which is one of the pivotal definitions in Q7, in my view. The risk to the quality and therefore, the safety and efficacy of the API, was low, until you got to that point. And that, I think, is the biggest risk-based approach that we took, because it took out a lot of unnecessary controls.

The synthesis if you are making a steroid, might have many stages depending on which steroid you are making. But in actual fact, there is very, very low risk until you get to the point where you have the steroid nucleus and that may be only three or four steps from the end of the synthesis. You can waste a lot of resources trying to control things that didn't need to be controlled before you got to that steroid nucleus, which would be the API starting material.

That was probably one of the things that helped industry the most, assigning the right level of GMP and control throughout the whole of a long synthesis. We gave guidance in the text for defining what is the API starting material.

PL: Gordon, you were the rapporteur for Q7. Would you like to make the final comment in our discussion and tell us what you thought of the team you led, which included Edwin?

GM: The Q7A team will always stand out in my memory as one of the best teams that I ever worked on. And considering how diverse the membership was both in terms of different countries, different backgrounds and technically different in some cases, it still became a very strong team. It is one that I am very proud to have been part of, and to have been part of producing the document. One of my lasting memories of Q7 is hard work, but lots of fun along the way in creating it.

PL: Great discussion. It was illuminating. Thanks to both of you for discussing this with us.

About the Experts

Gordon Munro, PhD, has served as the Senior Vice President, Quality Assurance of Watson Pharmaceuticals, Inc., since June 2004. Prior to joining Watson, Gordon was the Director of Inspection and Enforcement at the United Kingdom Medicines and Healthcare Products Regulatory Agency from 1997 to 2004, and from 2002 to 2004, he was also Acting Head of Medicines. From 1970 to 1997, he held various positions, including the Director of Quality and Compliance at GlaxoWelcome. He received a Bachelor of Science in Pharmacy, and a Masters in Analytical Chemistry from the University of Strathclyde, Scotland, and a PhD in Analytical Chemistry from the Council of National Academic Awards. Gordon was the rapporteur for the ICH Q7 expert working group.

Edwin Rivera-Martinez received his B.S. in Chemistry in 1976 and completed a MBA in 1986. He has worked for the U.S. FDA for over 30 years, first as an inspector in the San Juan district office and then in the Division of Manufacturing and Product Quality (DMPQ) in CDER's Office of Compliance. Most recently, he was appointed as Chief of the Manufacturing Assessment and Preapproval Compliance Branch. Edwin was a member of the Agency's API GMP Task Force charged with developing an FDA industry guidance document for the manufacture, control, and validation of APIs. He also served as the Agency's technical expert on the ICH Q7 Expert Working Group and was actively involved in its implementation, and training of both FDA and industry personnel on its contents and interpretation.

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Quality & Regulatory Snapshot

International Pharmaceutical *Quality*

Analysis of U.S. FDA, EU Authority Inspection Findings

Bill Paulson, IPQ

The May/June issue of *International Pharmaceutical Quality* provides an incisive, up-to-date analysis of recent U.S. FDA and EU authority inspection findings and enforcement actions.

The analysis reveals that:

- FDA warning letters and injunctions are frequently linking GMP problems with the manufacturing of products that do not have the required new drug approval or do not meet OTC monograph standards, as the agency's crackdown on the various types of unapproved drugs continues.
- Inadequate investigation of manufacturing and product nonconformances is the most pressing GMP concern on both sides of the Atlantic. Beyond just retraining, regulators are looking for a deeper understanding of the flaws in the quality system out of which operator errors stem.
- FDA's foreign warning letters are addressing the growing concern with supply chain control.
- The challenges of vaccine production are getting increased inspection attention as this product segment expands. Biological Product Deviation Reports are not always getting submitted on time and the FDA is concerned.

TYPES OF HUMAN ERRORS

At a recent conference, FDA National Drug Expert Investigator Rebeca Rodriguez pointed out that the effectiveness of training as a preventive or corrective action will depend on the type of human error that it is intended to prevent or correct. She commented on five different types of human error that are uncovered during inspections.

- **Organizational/systemic:** For example, when the work culture priority in the company is efficiency and productivity. Of course, efficiency and productivity are important, but so is quality. So there has to be a balance. Some companies put quite too much emphasis on productivity. And the managers lead by example and people are just cutting corners the same as the managers, and they are therefore taking product and regulatory risks to reduce cost and increase profits. And some companies have gone so far as to say that they would take the risk of doing this or that, because they don't expect FDA to catch them doing it.
- **Procedural (SOPs):** Sometimes SOPS are not clear, or the instructions are contradictory. I saw a company during an inspection that was having pretty serious problems with their cleaning procedures. They were having a lot of cleaning verification or evaluation sample failures. And sure enough when I went to the SOPs, they were not clear. When I interviewed the operators, they were doing different things. But it was not the operator's fault, it was the company's fault, because the SOPs were not clear in the first place. How do you train someone in SOPs that are not clear?
- **Careless work:** That is another type of human error, where people are forgetful. They are not paying attention to what they are doing, or they are careless. Sometimes people have serious personal problems, they have a lot of stuff in their minds. This happens. But also the work environment may have an influence on these types of errors. For example if you have an operation where you have to rely on the person's memory to execute some steps correctly, you [may be] setting that person up for failure.
- **Voluntary/intentional:** The SOP is inadequate and the employees know the SOP is wrong and they just don't follow it. Many times we see that employees do backdating, sometimes following instructions from managers.
- **Involuntary:** Errors due to human variability. We know there are going to be errors. We are just human. We are all human. But what can we do to minimize them? It depends on the type of error, as I said.

Also in this issue don't miss the "Voices from the Dialogue" featuring: MHRA GMP Inspector **Andrew Hopkins** on the top MHRA inspection findings, PAREXEL Consultant **David Chesney** on forces impacting FDA enforcement, and CDER compliance official **Joseph Famulare** on recent GMP injunctions, as well as a complete listing of FDA drug GMP warning letters issued in 2008 and 2009 through May.

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The Sterilisation Technology conference will review existing and future technologies for building and maintaining an adequate sterility assurance level when sterilising materials, components and finished bio/pharmaceutical products and medical devices within the healthcare industry. Presentations from industry and regulatory experts will cover the range of available technologies in current use, along with expected new approaches for the manufacture of e. g. sterile products, immediate containers or medical devices.

WHO Draft Consultation Update: GMP for Sterile Pharmaceutical Products

A Commentary on Divergence between WHO's Proposal and EU Annex 1

Martyn Becker, Martyn Becker Associates

The publication by the World Health Organization (WHO) of *Good Manufacturing Practices for Sterile Pharmaceutical Products: Proposal for Revision* (Document QAS/09.295) in May, is being made ostensibly to bring it into line with ISO 14644 on clean rooms, as indeed was EU Annex 1 in 2008. WHO is very influential because its GMP guidance is used by more than a hundred countries, primarily in developing nations. Historically, it has derived its GMP guidance from equivalent EU documents, and that link can be seen within the current document also.

On the surface, there are many similarities between the proposed WHO document and the EU GMP Annex 1 on sterile medicinal products from which it is clearly derived. Much of its actual content is seen to mirror Annex 1 almost exactly, for example, the sections on terminal sterilization, isolators, blow-fill-seal, dry heat/gaseous sterilization and sterile product finishing. Other sections are similar to the Annex 1 text, but with a number of important differences and realignments—and what is more significant, important *philosophical* realignments. Where the text is very similar, it does not in the main represent significant interpretational differences from Annex 1. In one case, this mirroring has resulted in the carry over of a mistake from the Annex 1 text involving the use of the term "sanitation." As defined, "sanitation" refers to toilet plumbing, whereas "sanitization" refers to the act of cleaning, which is the thrust of the section of the document titled, "sanitation." The same misuse of the word has been present in Annex 1 for some years.

There is however a clear difference to be seen elsewhere in this new draft. What WHO appears to have done is to expand and rethink specific concepts of Annex 1 and integrate them with thinking from other guidance documents on sterile products—specifically, with the U.S. FDA's thinking as described in FDA's 2004 guidance document, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*. This does at least three things:

1) It attempts to provide a level of harmony to different global perspectives on how to manufacture sterile products.
2) It veers the traditional European Union-centric view of its documents towards the FDA perspective.
3) If published in this form, it will veer a large proportion of the world's regulatory agencies that use the WHO documents as the basis for their GMP compliance along with them.

The future implications for this are large, and it is necessary to understand these philosophical changes.

Diverging from Annex 1

A review of the WHO proposal to revise its GMPs for sterile pharmaceuticals suggests that the organization has taken the opportunity to look at the sense and scientific logic of the Annex 1 requirements, and measure these up against what FDA requires in its own guidance rather than adopting the Annex 1 text wholesale. As a result, sometimes the path chosen is significantly different to that indicated by the European Union regulatory authorities.

WHO also has taken the opportunity to include some explanatory clauses or make explicit what in Annex 1 is implicit. For example, clause 2.3 in the WHO draft emphasizes sterilization validation and process simulation as fundamental to sterility assurance, and requires their results to be evaluated alongside sterility test results. This kind of statement is implied, but not actually defined in Annex 1. Even so, up to this point there is a harmony of wording and purpose between WHO and the European Union. It is in the sections on manufacturing that differences become apparent, and some of these differences have significant implications.

For instance, the Annex 1 clause requiring separation of product preparation, component preparation and filling into different physical areas is missing from the WHO document, which could lead to different design specifications for facilities, depending upon which document was being referenced.

One of the most significant philosophical differences between the documents is to be found here. Particulate monitoring is only specified at >0.5µ, rather than at >0.5µ, and at >5.0µ, which aligns the philosophy with that of FDA, which does not consider the monitoring of >5.0µ particles significant. WHO makes this perspective clear in the document's introduction. This perspective moves the WHO document significantly away from the European Union viewpoint and aligns with the FDA.

Clause 4.3 requires the use of ISO 14644-1 as does Annex 1.4.4; however, it provides another significant difference to Annex 1 in that whereas Annex 1 requires a homogeneous air speed of 0.45m/s +/-20% (it actually specifies 0.36-0.54 m/s which is the same thing) *at the working position*, the WHO document requires this air speed *at a distance of 15-30 cm below the filter face*. Many would argue this is more meaningful due to the application of inverse-square law. Simply put, many firms do not (and *cannot*) demonstrate compliance with the Annex 1 requirement since the height of the filter faces above the working position can be anywhere between 2 and 4 meters, and to provide that speed of unidirectional air at that distance would require hurricane force through the filter. The WHO requirement satisfies itself by the demonstration of unidirectional flow at that speed at a distance much closer to the filter, and is therefore potentially more achievable and reproducible. It is, however, not clear what the scientific justification for the selection of those particular distances is.

The WHO document also refers the reader to ISO 14644 for determination of sample volume for particles, whereas Annex 1 states a minimum 1m^3 sample. For particles >5.0µ with a grade limit of 20 particles a 1m^3 sample may be appropriate, whereas for >0.5µ particles only a significant difference in sample size will be calculated using the example calculations in ISO 14644 (Annex D).

As discussed above, clauses 3.1-3.3 mirror Annex 1's clauses 61 and 62 on sanitization, but with some significant additions—these being: the non-use of UV light in preference to chemical disinfection and the requirement for a sporicidal agent in facility cleaning. There is also a change of wording which could lead to conflicting interpretations and subsequent requirements: WHO requires Grade A/B disinfectants to be "sterilized" prior to use, whereas Annex 1 requires them to be "sterile" prior to use. A subtle distinction that has the potential for confusion. Annex 1 clause 63 on fumigation is not reproduced in the WHO document, indicating that it may not normally be sanctioned.

Clauses 3.4-3.5 requires microbiological monitoring for demonstration of maintenance of microbiological cleanliness, found in Annex 1 clause 18. Clause 3.5 states that the numerical values in the appropriate table (table 4 in the document) are not specifications, but are for information only. Annex 1 at clause 19 states that its figures are indeed limits, which need to be investigated if exceeded.

The aseptic preparation section is practically identical to Annex 1 to the extent that what appears to be of the largest editorial errors in the recent edition of Annex 1 is exactly reproduced in the WHO document. WHO clause 4.21 allows the transfer of partially-stoppered vials in sealed trays through Grade B, as does clause 34 in Annex 1. However, 13.1 requires maintenance of partially-stoppered vials under Grade A "at all times"—exactly the same wording as in Annex 1 clause 116. Both documents; therefore, set different requirements for this activity in different parts of the document.

Product filter sterilization requirements are similar to Annex 1 with a significant difference at 7.7, where the requirement is for "the integrity of the filter" to be checked prior to sterilization, whereas Annex 1 specifies integrity of the "sterilized filter," again, a source of potential divergence in interpretation.

The equipment section is largely aligned with Annex 1. However, clause 12.6 requires >70°C for WFI recirculation as does Annex 1; however, it also offers an alternative of <4°C. Other more minor changes are captured in the table below.

Moving Ahead

Looking at the differences between the WHO document and its Annex 1 parent, several points seem clear. The significant differences indicated above move the philosophy of WHO closer to that of FDA, particularly with respect to the lack of >5.0µ particle monitoring and the attendant smaller sampling volumes associated with this as defined by the ISO 14644 calculations.

There are implications in this that only time will or will not confirm. With the WHO document moving more towards the FDA standpoint, we are likely to see a situation where FDA and WHO might represent one side of a global philosophical position on sterile product manufacture, and European Union, Pharmaceutical Inspection Cooperation Scheme (PIC/S) and those countries that have used the European Union guide as a basis for their own GMPs on the other. Given that the European Union has firmly indicated its adherence to the >5.0µ issue in particular, some constructive and persuasive discussion needs to be held to enable these sides to move

At a Glance: Differences Between WHO Proposed GMPs and EU Annex 1

Major differences:

- Does not require physical separation of component preparation, product preparation and filling, thereby potentially leading to different design philosophies.
- Particulate monitoring at >0.5μ only. This level of particle monitoring is not required, potentially leading to divergent practices regarding sample volumes and significance of particles detected. Sample volume is determined by calculation for >0.5μ particles according to ISO 14644, which is significantly less than the 1m^3 required by Annex 1.
- Unidirectional air velocity monitored 15–30 cm from filter face rather than at working position.
- Requirement for personnel to be excluded from Grade A areas, which is not mandated by Annex 1 and would be very difficult to implement.
- Integrity of filter required to be demonstrated rather than the integrity of the sterilized filter.
- Microbiological monitoring figures for information only, rather than limits.

Minor differences:

- Apparent removal of parametric release from consideration.
- Chemical disinfection preferred to UV light.
- Use of sporicides required in facility disinfection.
- Disinfectants "sterilized prior to use" rather than being "sterile prior to use."
- Minimum 20 air changes per hour required in Grade A.
- Clothing restrictions in changing rooms.
- Avoid unnecessary entry of control or supervisory personnel into Grade A/B.
- Grade B areas designed to that operations can be seen from outside.
- Segregation of personnel entering and exiting changing rooms.

closer together philosophically before they start to drift further apart.

There is also a driver for why this process needs to happen, and soon. This is simply because FDA has applied to join PIC/S, and membership of PIC/S requires the acceding country to adopt the PIC/S guide as its code of GMP. In its current condition, the PIC/S guide to sterile products is a virtual copy of the EU GMP Annex 1, so it is unlikely to be acceptable to FDA, which is known to be antipathetic to a number of the philosophical contents of Annex 1. FDA is therefore more likely to be sympathetic to the contents of the WHO sterile guide since it is much more aligned to their philosophy. This of course does not consider the legal status of how easy it would be to modify or change the U.S. GMPs as defined in the Code of Federal Regulations.

There are a number of issues that will need to be clarified from a technical, logical and scientifically supportable standpoint...

There are a number of issues that will need to be clarified from a technical, logical and scientifically supportable standpoint, not the least of which will be frank discussion on the sources of some of the different requirements in the European Union and WHO documents. As for one example, let us take the largest issue, that of the monitoring of >5.0µ particles. The "for" lobby maintains that the monitoring of this size of particle is fundamental to the understanding of the health of the facility's air supply system, and that significant numbers of particles detected means a facility issue—even if there is not a correspondingly large number of >0.5µ particles. The "against" lobby points out that research from the past ten years indicates that there is indeed such a correlation so that monitoring at the larger size is not relevant. Such diametrically opposed viewpoints require the provision of information to be able to decide which one is scientifically correct, since they both cannot be. If it is true that there was no correlation, and >5.0µ particle monitoring is essential, why make it a formal requirement instead of requiring that a firm demonstrates its capability of demonstrating the fitness of its installation? European Union regulators have not been forthcoming with scientific support for their position. On the other hand, if it is true that there is a correlation, and that you can predict facility health from >0.5µ particle monitoring alone, then why not make specific reference to this in the opening introduction to the WHO document? It refers to "experts," but makes no reference to who these might be.

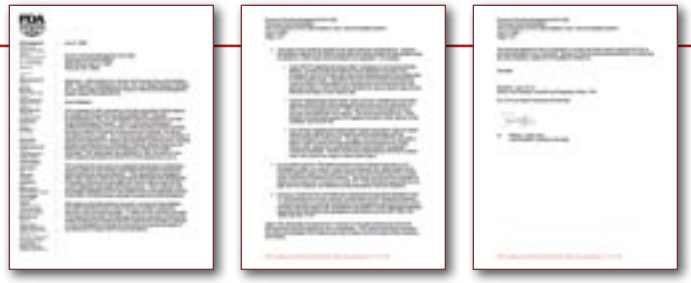
In reality then, this WHO document (or something similar to it) could be key in getting both sides of the philosophical debate around a discussion table to talk about practical scientific support for philosophies that might make a world of difference to the way that our industry manufactures aseptically produced sterile products. They might then also be able to come to consensus on a single philosophy that will be necessary for FDA to accept the PIC/S guide. If that were all possible, the harmonization produced would certainly provide many benefits for the industry that the regulatory bodies serve.

Conclusion

It seems clear that this iteration of the WHO sterile products guidance document has been developed with the intent of using the framework of EU GMP Annex 1 to build a document that incorporates other philosophies, and therefore potentially serve as some kind of bridge to harmonization with other GMP environments that otherwise may not have been possible with Annex 1. Reference is specifically made here to FDA GMP regulations as set down in 21 CFR, Parts 210 and 211, and their guidance equivalents such as the 2004 aseptic processing guidance since there are certainly blockages to harmonization as things currently stand. Although the bulk of the WHO guidance is very close to (and identical with in many cases) Annex 1, listed to the left are the significant differences to Annex 1 that set it apart from the European position and move it closer to the FDA philosophy.

PDA's Comments Address Concerns About Injector Draft Guidance

For the comments grid, visit www.pda.org/regulatorycomments.



July 27, 2009

Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Reference: Draft Guidance for Industry and Food and Drug Administration Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use With Drugs and Biological Products; Federal Dockets Management System Docket FDA-2009-D-0179

Dear Sir/Madam:

PDA is pleased to offer comments on the document titled "Draft Guidance for Industry and Food and Drug Administration Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use With Drugs and Biological Products". PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in injector and combination product issues, including members representing our Combination Products Interest Group and our Biotechnology Advisory Board and Regulatory Affairs and Quality Committee. PDA appreciates the opportunity to offer comments on this Draft Guidance and wishes to thank FDA for the opportunity to do so.

PDA embraces this document as a significant step forward in addressing industry questions and concerns associated with Injectors and assuring these products are safe and effective. PDA applauds this interagency effort which seeks to clarify the requirements associated with development of regulatory submissions associated with various injector types and the unique challenges associated with these products. PDA is willing to offer any possible assistance to FDA and indeed to any of the agencies involved in this effort in furthering these important concepts and recommendations.

With regard to the draft guidance document, we have provided detailed comments identified by line number and have included a supporting rationale in the accompanying table. In addition to the comments provided in the attached document, the following comments represent overall points noted throughout the Guidance that PDA believes are important to address in order to strengthen this guidance document and improve the ability of manufacturers to comply with its recommendations:

- The scope of the Guidance appears to be quite broad and comprehensive. However, the guidance offered on the various topics does not clearly identify the appropriate scope or situations in which these recommendations are applicable. For example:
  - o Lines 239-272 regarding the section titled "Comparison to an Existing Delivery Method," include a broad and extensive list of attributes to include in this comparison, but do not clarify that some of the attributes would not be applicable to certain Injector types. We believe that the current content and format may cause confusion in interpretation by manufacturers and recommend that FDA generate a table or matrix that clearly identifies the various Injector types and the attributes that apply to each Injector type.
  - o Line 610 regarding the section titled "Dose Accuracy" indicates that multi-dose injectors should confirm that subsequent doses are same as initial dose, but does not acknowledge that ISO 11608 requirements should apply for dose accuracy associated with Pen Injectors. We recommend that the ISO 11608 standard and associated scope of its usage be included in other sections of the Guidance, such as line 443.
  - o Line 104-230, regarding the section titled "Injector Description" does not clearly identify which Injector types or situations would be associated with the recommendations of this section. We again recommend that FDA generate a table or matrix to clarify the recommendations as they apply to the unique Injector types, taking into consideration the Injector types in recognized consensus standards. We also recommend explaining how the terms "product class" and "product line" apply to these Injector types.

We would be pleased to offer our expertise in a public discussion and/or meeting with FDA to provide clarification of our comments. Should you wish to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely,
Richard V. Levy, PhD, Senior Vice President, Scientific and Regulatory Affairs, PDA

Regulatory Briefs

Regulatory briefs are compiled by PDA member volunteers and staff directly from official government/compendial releases. Links to additional information and documentation are available at http://www.pda.org/regulatorynews.

International Conference on Harmonisation

Four Pharmacopoeia Methods Deemed Interchangeable Per ICH Q4B Annexes

In June, the International Conference on Harmonisation (ICH) announced progress in four important compendial standards under the Pharmacopoeial Discussion Group process.

Reaching Step 5 were *Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Disintegration Test General Chapter* (ICH Q4B Annex 5), and *Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Sterility Test General Chapter* (ICH Q4B Annex 8).

Reaching Step 3 were *Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Tablet Friability General Chapter* (ICH Q4B Annex 9), and *Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Polyacrylamide Gel Electrophoresis General Chapter* (ICH Q4B Annex 10).

According to the ICH, the above annexes are "interchangeable" in the ICH regions.

Europe

EMEA Guideline on Human Cell-Based Medicinal Products Released

The EMEA's Committee for Medicinal Product for Human Use has released a guideline, entitled, *Human Cell-Based Medicinal Products,* that takes into account the current legislation and the heterogeneity of human cell-based products, including combination products.

In the quality and manufacturing section assistance is provided on the criteria and testing of all starting materials on the design and validation of the manufacturing process; the characterization of the human cell-based medicinal products; quality control aspects; the development program; traceability and vigilance; and on comparability issues.

This guideline replaces the *Points to Consider on the Manufacture and Quality Control of Human Somatic Cell Therapy Medicinal Products* guidance.

EMEA's Guideline Specifies Procedures with Pandemic Influenza Vaccine Application

Adopted in November 2006, and revised on June 25, 2009, the EMEA's Committee for Medicinal Products for Human Use (CHMP) guideline on dossier structure and content for pandemic influenza vaccine marketing authorization application specifies that marketing authorization holders should have protocols in place at the time of authorization of the mock-up vaccine. This will ensure that immunogenicity, effectiveness and safety of the final pandemic vaccine are adequately documented during use in the field (i.e., during the pandemic), since there will be only limited immunogenicity and safety data, and no efficacy data at the time of licensing.

The document provides recommendations on how routine and additional pharmacovigilance activities should be conducted during the pandemic period, as well as the preparatory activities to be undertaken in the pre-pandemic period to achieve a high level of preparedness.

The pandemic influenza pharmacovigilance plan will terminate when it has been agreed with national competent authorities that it is no more necessary.

EMEA's Amendments Affect Marketing Authorization for Medicinal Products

EMEA has published amendments to two directives affecting the terms of marketing authorizations for medicinal products. This is part of a global revision of the legal framework on variations to make the overall system clearer, simpler and more flexible. It amends the legal basis for the adoption of the European Community rules on variations in order to harmonize those rules for all authorized medicines in the EU.

Directive 2009/53/EC of the European Parliament and of the Council of June 18, 2009, published in the Official Journal on June 30, 2009, amends Directive 2001/82/EC and Directive 2001/83/EC.

Australian Parliament Looking to Build New Biologics Regulatory Framework

The Therapeutic Goods Administration (TGA) has begun preparing for possible amendments to the regulatory framework for biological drug products, in anticipation of pending legislation.

The Australian Parliament is currently considering a bill entitled, the Therapeutic Goods Amendment Bill 2009, which will include amendments to biologics regulations.

TGA is looking at its product standards and GMP regulations to ensure that these will operate together as intended. In particular, focus is currently being given to the Infectious Disease Standard.

The bill is expected to be introduced in Parliament in the session beginning August 11, 2009. Should the bill pass, the goal is for it to begin in 2010 with transition arrangements provided for over a subsequent three year period as agreed by Commonwealth, state and territory health ministers in 2006.

North America

U.S. FDA Guidance Aides Adverse Event Reporting Compliance

The U.S. FDA has announced the availability of a guidance entitled, *Questions and Answers Regarding Adverse Event Reporting and Record Keeping for Dietary Supplements as Required by the Dietary*

Supplement and Nonprescription Drug Consumer Protection Act. This document provides guidance to the dietary supplement industry in complying with the serious adverse event reporting and record keeping requirements prescribed for dietary supplement manufacturers, packers and distributors by the Dietary Supplement and Nonprescription Drug Consumer Protection Act.

U.S. FDA Publishes Guidance on Postmarketing Serious Adverse Event Reporting

The U.S. FDA has announced the availability of a guidance entitled, *Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application.* This document provides guidance to industry on postmarketing serious adverse event reporting for non-prescription over-the-counter human drugs marketed without an approved application.

U.S. FDA Draft Guidance Incorporates Identifiers into Solid Oral Dosage Form

The U.S. FDA has announced the availability of a draft guidance for Industry entitled, *Incorporation of Physical-Chemical Identifiers into Solid Oral Dosage Form Drug Products for Anticounterfeiting.*

The draft guidance provides recommendations to manufacturers on design considerations for incorporating physical-chemical identifiers into solid oral dosage forms; supporting documentation to be submitted in NDAs and ANDAs to address the proposed incorporation of these identifiers; supporting documentation to be submitted in post approval submissions to report or request approval to incorporate such identifiers; and procedures for reporting or requesting approval to incorporate these identifiers into solid oral dosage forms as a post-approval change.

The draft guidance also provides recommendations regarding evaluation of toxicological and other concerns for identifiers that are incorporated into packaging and labeling, and procedures for reporting or requesting approval to add identifiers to packaging and containers as a post-approval change.

Comments may be submitted by October 13, 2009.

U.S. FDA Guidance to Assist with the Process of IRB Registration

The U.S. FDA has announced the availability of a guidance entitled, *Guidance for Institutional Review Boards (IRBs), Frequently Asked Questions – IRB Registration."* This guidance is intended to assist IRBs in complying with the new requirements for registration.

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology to Hold Meeting on Variable Drugs

The U.S. FDA has announced that the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology will have a meeting on August 5.

At the meeting, the Committee will receive a status update from the Office of Generic Drugs on bioequivalence for highly variable drugs; receive presentations from the Office of Pharmaceutical Science (OPS) on the scientific and regulatory challenges of Transdermal Drug Delivery Systems; receive presentations from OPS and discuss current thinking on "Classifying Pre-Surgical Preparations as Sterile Products" in consideration of how these products are used; and be updated by OPS on the current status of the International Conference on Harmonization Quality Topics (i.e., those relating to chemical and pharmaceutical quality assurance stability testing, impurity testing, etc.), and outline the role of the ICH Implementation Work Group.

The meeting will take place at the Hilton Washington D.C./Silver Spring, The Ballrooms, 8727 Colesville Road, Silver Spring, Md. Contact Paul Tran at 301–827–7001, or at paul.tran@fda.hhs.gov for more information.

U.S. FDA Guidance on ANDA's Available

The U.S. FDA has announced the availability of a guidance entitled, *ANDAs: Impurities in Drug Substances.*

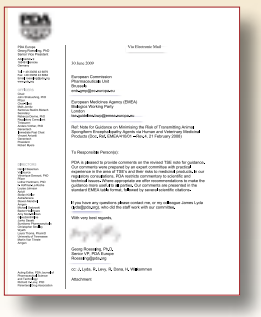
The guidance provides recommendations for applicants on what chemistry, manufacturing and controls information to include regarding the reporting, identification and qualification of impurities in drug substances produced by chemical synthesis when submitting original abbreviated new drug applications (ANDAs), drug master files and ANDA supplements for changes in the synthesis or processing of drug substances.

The guidance revises the November 1999 Guidance of the same name.

Draft Guidance Provides Information about Implementation of 2007 FDAAA

The U.S. FDA has announced the availability of a draft guidance entitled, *Postmarketing Studies and Clinical Trials – Implementation of [Section 505(o) of] the Federal Food, Drug, and Cosmetic Act.* The draft guidance provides information on the implementation of new provisions of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and a description of the types of postmarketing studies and clinical trials that will generally be required under the new legislation.

Comments on the draft guidance must be submitted by October 13, 2009.



PDA has commented on the draft guidance *Technical Considerations for Pen, Jet and Related Injectors Intended for Use with Drugs and Biological Products*, see page 29.

PDA has also commented on EMEA's *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*. To see PDA's comments, go to www.pda.org/regulatory comments.

PDA Tools For Success

Finding the Upside in the Economic Downturn

Theresa Rose

Yep, it's really bad out there. It seems like not a day goes by without another story of doom and gloom hitting the airwaves or whispered around the water cooler. We are living in the most challenging time in recent memory: people across the country are losing their health insurance, jobs, homes and retirement savings. The negative effect of the current circumstances in which we live—both on a financial and an emotional level—cannot be underestimated. Unfortunately, there is not a lot we as individuals can do to change the global financial system. However, constantly reminding ourselves of how uncertain our future is does a great disservice to our professional lives as well as wreaks havoc on our attitudes, relationships and health.

Despite the bleak forecasts, all is not lost. In fact, contrary to conventional wisdom, the financial crisis may actually contain several profound benefits buried beneath the bad news. If you want to survive the economic maelstrom with your job, relationships and health intact, consider acknowledging the potential gifts the downturn has provided:

1 Clarifying Priorities

There's no doubt about it; the wake-up call has been made. We have been forced to reevaluate what truly matters. What is really important to you right now? Is it the big house filled with big stuff or the precious people in your life? Is it the numbers on the 401(k) account statement or your blood pressure numbers? Is the Monthly TPS Report really worth fretting over? By realizing that our health and family are far more important than anything else, we are able to separate distractions from necessity. What good is obsessing over our jobs if the price we are paying is our well-being and relationships?

2 Making Better Choices

Our tighter wallets are forcing us to consume less and conserve more. Recycling and reusing are becoming more than popular catchphrases; they have become an integral part of our everyday lives. We are driving less in order to save on gas, eating last night's leftovers for lunch instead of going out to eat and being more conscious of what we throw away. Whether it is an overhaul of all business expenditures or simply refilling the printer toner instead of buying a new one, this unintended shift of consciousness is not only benefiting our financial future but also the health and sustainability of the Earth.

3 Staying Put

Many people are enjoying "staycations" as opposed to vacations, opting to spend quality recreational time at home or nearby. Investigate the local attractions you and your family can check out on the cheap. Is there a state park you have heard about but haven't yet visited? Maybe the local high school or college is putting on a theatre production that you and your spouse would enjoy. Embracing the pearls found within our local communities is giving our pocketbooks a much-needed rest and reminds us that we don't have to escape our current environment to have fun.

4 Feeling More Interconnected

Everyone is feeling the pain of our national crisis; there is no longer a nameless, faceless "other" who is affected. Not unlike the unheralded unity created after 9/11, the national rocky road we are all traveling upon is helping to create a deeper camaraderie. We have moved away from the "me, me, me" mentality toward a "me too" one. By experiencing this journey together, we are more compassionate toward our fellow Americans than ever before.

5 Getting Better

This is the perfect time to build upon your skill set. What technical skills can you brush up on to solidify your organizational value or make yourself more marketable? How about dusting off your favorite hobby and turning it into an additional income source? There is a multitude of hidden opportunities for growth and prosperity if we open ourselves to it.

6 Expressing gratitude

No matter how bad the situation, we can always find things to appreciate in our lives. Ask yourself the following questions: Do you have a job? Do you have a home? Do you have people who love you? Are you healthy? Sometimes we need major difficulties to remind us of how rich we truly are. It doesn't take very much effort to find someone who has it worse than you. Now is the ideal time to be grateful for the countless blessings.

This moment offers us a chance to move into uncharted territory instead of shrinking into the collective fear. Now is the time to discover the best of who we are, not allow the worst of ourselves to appear. When we shift our inner focus from depression to appreciation, everything around us begins to change as well. We no longer get trapped in our own misery. Our family and friends become our strongest allies. Our employers see us as part of the solution instead of another problem to manage. Our

outlook becomes hopeful instead of hopeless. We position ourselves at the forefront of the recovery effort. Most importantly, we realize that we are responsible for our own happiness, not the latest economic report or a sound byte from a cable news show. *Remember: this too shall pass.* How do you want to experience this critical juncture? Do you want to be full of fear or full of joy?

About the Author:

Theresa Rose is an inspirational speaker and award-winning author of the new book, *Opening the Kimono*. As the founder of Serious Mojo Publications, Theresa specializes in fresh approaches to energy management, productivity and creative development. Her experience includes owning a healing center, senior manager of a Fortune 100 firm, and vice president of a consulting firm. For more information, visit www.TheresaRose.net.

Send in your feedback on *Tools for Success* section. Email Emily Hough at hough@pda.org.

Recommended Reading

Steam Sterilization: A Practitioner's Guide, Jeanne Moldenhauer, Ed.

This book contains pragmatic details on how to accomplish the tasks necessary for a sterility assurance program for steam sterilization processes.

To order this book and more, visit www.pda.org/bookstore

Recipients of the 2008 Honor Awards:

Distinguished Service Award

www.pda.org/2008honorawards

The honor awards have been bestowed to esteemed PDA members since the first award was given in 1958. It is our intention to highlight the 2008 Honor Award Winners who were recognized at PDA's Annual Meeting banquet. **[Editor's Note:** We have selected four of PDA's 2008 awardees to highlight in this issue. Be sure to look at this section in future issues for additional winners! You can also access this online at www.pda.org/2008honorawards**]**

Distinguished Service Award

This award is given in recognition of special acts, contributions or services that have contributed to the success of PDA. For 2008, seven members received the award, three of whom will be highlighted in the next issue.

Recipient: Myron Dittmer

Reason Received Award:

Myron has been a PDA member since 1984, making significant contributions to the PDA New England Chapter through his consistent and steady leadership. Myron has held several chapter officer positions including: President, President-elect, and Member-at-Large, and is a founding member of the New England Chapter. Most recently, Myron has been nominated as co-chair of the PDA's Chapter's Council, and he remains an active contributor to the success of the New England Chapter.

Recipient: Mathias Romacker

Reason Received Award:

Mathias helped start the first conference of *The Universe of Pre-Filled Syringes.* Mathias actively contributed to the conference in Europe and the United States, and he is an active member in the Pre-filled Syringes Interest Group.

Recipient: Daikichiro Murakami

Reason Received Award:

Daikichiro is the Japanese liaison between the western countries and the Japan PDA Chapter. He is known for his membership outreach efforts, and his involvement with local conferences as a speaker liaison. He most recently worked on the Visual Inspections conferences.

Recipient: Thomas Schoenknecht, PhD

Reason Received Award:

Thomas helped initiate the first conference of *The Universe of Pre-filled Syringe.* Thomas was one of the founders of the Pre-filled Syringe Interest Group, and was its leader in Europe for the first years. He is currently the leader of the Pre-filled Syringe Interest Group in the United States. He has been the conference chair of *the Universe of Pre-filled Syringe* meeting, and continuous to be very active in this field as a taskforce leader.

Distinguish yourself! Join a chapter or a task force. Learn about all PDA volunteer opportunities at **www.pda.org/getinvolved**

Volunteer Spotlights

Read more about our volunteers at www.pda.org/spotlight

Bryan Riley, PhD

Senior Review Microbiologist, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Education: BS, Microbiology, Texas Tech University, 1981; MS, Microbiology, Texas Tech University, 1985; PhD, Microbiology, University of North Texas, 1989

PDA Join Date: 1998

Areas of PDA Volunteerism: Speaker at numerous PDA Conferences and Workshops; PDA Technical Report No. 33, *Evaluation, Validation and Implementation of New Microbiological Testing Methods* Task Force (member); Program Planning Committee Member for PDA's Annual Global Conference on Pharmaceutical Microbiology (Co-chair 2007 and 2009)

Why did you join PDA and start to volunteer? After speaking at PDA Conferences, I wanted to get involved in some of the other activities that PDA offers. Participating in the working group to revise PDA Technical Report No. 33, *Evaluation, Validation and Implementation of New Microbiological Testing Methods* and being on the program planning committee for the Annual Global Microbiology Conference appealed to me as ways to contribute to PDA's scientific and technical outreach. I've always enjoyed attending PDA conferences, and have often used PDA Technical Reports as valuable reference materials.

How has volunteering through PDA benefited you professionally? My activities with PDA have allowed me to meet people throughout the global pharmaceutical industry which has been very useful. It is very nice to interact with people on a more informal basis through PDA, rather than my usual contact with them as a regulator.

Which member benefit do you most look forward to? Receiving the *PDA Journal of Pharmaceutical Science and Technology*.

Which PDA event/training course is your favorite? I would have to say it's the Annual Global Conference on Pharmaceutical Microbiology. As a microbiologist, this is the most useful and interesting meeting for me to attend. The opportunity to learn from the experiences of other microbiologists is unmatched in my opinion. There are also numerous opportunities throughout the conference to meet new people and catch up with old friends.

What would you say to somebody considering PDA membership? Being a member of PDA presents opportunities for professional development on multiple levels. Attendance at PDA conferences, workshops and courses provides a great deal of useful information and the opportunity to make invaluable professional contacts. Being a member of a PDA working group or program committee offers the chance to be a positive influence on the pharmaceutical industry that will be felt far beyond your own work environment.

Siegfried Schmitt, PhD

Principal Consultant, Parexel

Education: PhD, Organic Chemistry, University of Bern, Switzerland; Chartered Chemist (1997) and Chartered Scientist (2004), Royal Society for Chemistry

PDA Join Date: 2005

Areas of PDA Volunteerism: UK Chapter President (June 2007-present); Technical Book Advisory Board (2004-present)

Professional Awards: Winner of the PDA Distinguished Editor/Author Award 2008

Interesting Fact about Yourself: I am fond of reptiles, particularly snakes. Once I had the "pleasure" of swimming with two spitting cobras in a rock pool in Namibia's desert.

Why did you join PDA and start to volunteer? It all started when I was invited to present at the PDA International Congress in Rome in 2005. There was such a fantastic atmosphere with people passionate about good science, openly sharing ideas and views with industry and regulators. Plus, one was made to feel welcome, like they were part of a big family. There was no doubt that I wanted to be a member of PDA.

Later, Georg Roessling, PDA's European VP, approached me about becoming more active, which then led to me becoming PDA's UK Chapter President. In addition, I like to help with the organization of meetings, like the eminent event on Quality by Design (QbD) this September in Frankfurt.

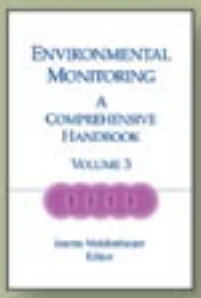
Of your PDA volunteer experiences, which stand out the most? Working with a team of enthusiastic and committed people on the UK Chapter board has to be the most outstanding experience. Through teamwork we have managed to establish a series of half-day events throughout the UK. These are becoming more popular and we get splendid support from industry, as we like to offer site tours if possible. And, at less than $30 they are superb value. This is a great example that shows that PDA listens to its members and their needs. Because of companies limited funds, and to limit members' time away from work, these half-day courses just fit the bill.

How has volunteering through PDA benefited you professionally? Of course, there is the element of staying current with scientific and regulatory developments. However, for me the biggest benefit comes from the extensive networking opportunities PDA provides. The industry has gone truly global, and being connected through an organization with worldwide reach is really essential for my work. In fact, actively engaging and participating in organizations, such as PDA, is part of my job description.

New Releases
from the PDA Bookstore

Check out these newly released titles in the PDA Bookstore, your source for pharmaceutical and biopharmaceutical science, technology and regulatory information.

PDA-DHI Publication



Environmental Monitoring: A Comprehensive Handbook, Volume 3
Edited by Jeanne Moldenhauer
Item No. 17285
Member: $335, Nonmember: $419
Bundle of Volume I, 2, 3, and protocol CD
Item No. 17286
Member: $845, Nonmember: $1049

SEPTEMBER FEATURED TITLES

Ethylene Oxide Sterilization: Validation and Routine Operations Handbook
By Anne F. Booth
Item No. 17276, Member: ~~$225~~ $195, Nonmember: $279

Quality Assurance Workbook for Pharmaceutical Manufacturers
By Michael Jahnke
Item No. 17240, Member: ~~$250~~ $220, Nonmember: $309

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These are a series of training programs using FDA's Guidance Document on the Production and Control of Sterile Drug Products Produced by Aseptic Processing and FDA's current thinking on GMPs for these operation. It covers 11 specific topics and separated into 6 CDs.
Item No. 11090, Member: $900, Nonmember: $1080
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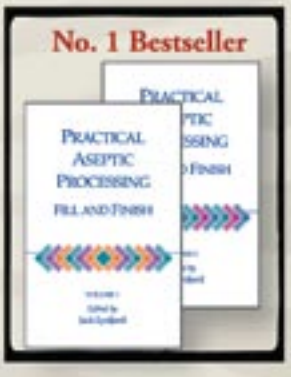
www.pda.org/bookstore

August Top 10 Bestsellers

1. **Practical Aseptic Processing: Fill and Finish, Volume I and II**
   Edited by Jack Lysfjord
   Item No. 17283, PDA Member $425, Nonmember $530
2. **Anatomy of a Pharmaceutical Filtration Differential Pressures, Flow Rates, Filter Areas, Throughputs and Filter Sizing - NEW!**
   By Theodore H. Meltzer, PhD and Maik W. Jornitz
   Item No. 17261, PDA Member $250, Nonmember $309
3. **Environmental Monitoring: A Comprehensive Handbook, Volume 3 - NEW!**
   Edited by Jeanne Moldenhauer
   Item No. 17285, PDA Member $335, Nonmember $419
4. **Water Activity Applications in the Pharmaceutical Industry - NEW!**
   Edited by Anthony M. Cundell, PhD and Anthony J. Fontana, Jr., PhD
   Item No. 17249, PDA Member $250, Nonmember $309
5. **Microbiology in Pharmaceutical Manufacturing, Second Edition, Revised and Expanded, Volume I and II**
   Edited by Richard Prince, PhD
   Item No. 17280, PDA Member $375, Nonmember $465
6. **Encyclopedia of Rapid Microbiological Methods, Volume I, II and III**
   Edited by Michael J. Miller, PhD
   Item No. 17252, PDA Member $795, Nonmember $989
7. **Pharmaceutical Quality Control Microbiology: A Guidebook to the Basics**
   By Scott Sutton, PhD
   Item No. 17242, PDA Member $235, Nonmember $289
8. **Understanding GMP: A Practical Guide - 50% Off**
   By Martyn Becker
   Item No. 17174, PDA Member ~~$225~~ $113, Nonmember ~~$279~~ $140
9. **Risk Assessment and Risk Management in the Pharmaceutical Industry: Clear and Simple**
   By James L. Vesper
   Item No. 17219, PDA Member $255, Nonmember $319
10. **Cleaning Validation: Practical Compliance Solutions for Pharmaceutical Manufacturing**
    By Destin A. LeBlanc
    Item No. 17253, PDA Member $265, Nonmember $329



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Chapter Contacts

The following is a list of the PDA Chapters, organized by the regions of the world in which they are located. Included are the Chapter name, the area(s) served, the Chapter contact person and his or her email address. Where applicable, the Chapter's website is listed. More information on PDA Chapters is available at www.pda.org/chapters.

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Peter Kitz, Merck

Timo Krebsbach, Labor L+S

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Daniel Yang, Taiki-sha

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David Yen, Baxter

Kuo-Wei Yin, Shin-Kong Memorial Hospital

Toshio Yoshida, Hisamitsu Pharmaceutical

Mitsunobu Yoshida, Astellas

Carole Youmbi Yamdjeu, Lonza

Jeong Young Kou, Pall

Chi Fang Yu, Taiwan Biotech Co.

Airy Yu, Adimmune

Te-Yueh Yu, Kuang Nan Pharmaceutical

Vincent Yu, Sunway Scientific

Shih Hung Yu, King To Nin Jiom Medicine Maf. Co.

Tai-Li Yu, Department of Health

Quei Mine Yuan, Hui Chun Tang Pharma. Works Co.

Tatung Yuan, Development Center for Biotechnology

Jack Zucker, Medarex

If your information appears inaccurate in this list, please visit www.pda.org to update your profile or email changes to info@pda.org.

Bring Your Questions for the Regulators: Expanded Discussion Time at the PDA/EMEA Joint Conference

Berlin, Germany • October 13–14 • www.pda.org/emea2009

Conference Committee Co-chairs Katrin Nodop, EMEA; Regine Leo, GMP Inspectorate Hannover, Germany; Véronique Davoust, Pfizer

PDA and the EMEA welcome you to the *2009 PDA/EMEA Joint Conference.* Planning for this year's conference began in July 2008 with the support of our Scientific Planning Committee (see right). As the outcome of that effort, we have prepared a fresh and exciting conference experience with the theme, *"Ensuring patient safety through supply chain control and GMP,"* which touches on traditional GMP and GDP concerns, as well as new issues facing both the pharmaceutical industry and regulatory authorities. We have listened to your comments and evaluations, and have structured the agenda in a way to allow more time for questions, answers and discussion.

The conference will open with plenary sessions to introduce the theme and cover topics which are of universal interest. The heart of the conference will consist of three parallel tracks, starting at lunch on Tuesday, and running until lunch on Wednesday. Each track consists of four sessions, each with a dedicated session chair to guide the discussions. To enhance each track, a committee sponsor volunteered to work with the session chairs to coordinate the content and speakers. The parallel tracks and sponsors are:

- *Supply Chain Quality,* **Véronique Davoust,** Pfizer
- *Implementation of ICH Q8–9-10,* **Liam Murphy,** Amgen
- *Manufacturing & GMP,* **Martyn Becker,** Martyn Becker Associates

The Wednesday afternoon plenary session will feature summary reports for all three tracks, an executive management view of the value of quality and perspectives from the EMEA on enhancing international cooperation. The closing session will have an interactive panel of regulator and industry leaders on the issues of the day, and perspectives on the future. The team who designed this exciting program share the same challenges and rewards in their work as you. Rarely will you have so many leaders presenting their views. So, we invite you to join us for these special two days.

Scientific Planning Committee

Thomas Barthel, Boehringer Ingelheim

Martyn Becker, Martyn Becker Associates

David Cockburn, EMEA

Anita Derks, F. Hoffmann-La Roche

Vjaceslavs Krauklis, State Agency of Medicines, Lativa

Karl-Heinz Menges, Regierungspräsidium Darmstadt, Germany

Liam Murphy, Amgen

Tesh Patel, Astellas Pharma

Annie Rietveld, Health Care Inspectorate, The Netherlands

Ian Thrussell, MHRA, United Kingdom

Cutting-Edge Technology on the Agenda for PDA Micro Conference

Bethesda, Md. • October 5-8 • www.pda.org/microbiology2009

Conference Program Planning Committee Member Ed Tidswell, PhD, Baxter

There's a new energy and impetus changing how we operate in the field of pharmaceutical microbiology. More specifically, how we manage the microbiology lab (instrumentally and in terms of process flow); how we design, monitor and control the microbiology of manufacturing processes; and how we disposition therapies and medical devices. Charting a course of improved economy, efficiency and expediency in "all things microbiological" is only navigable with the assistance from an increasing understanding of fundamental microbiology, microbial physiology, new innovations and the commercial realization of new laboratory and manufacturing floor technology. It is therefore fitting that *PDA's 4th Annual Global Conference on Pharmaceutical Microbiology,* focuses on novel analytical technologies and the movement of microbiological testing from the laboratory to the manufacturing environment, in other words, *Bringing Microbiology to the Manufacturing Floor.*

This theme is exemplified in both conference keynote addresses by globally recognized experts. First, **Roy Goodacre,** PhD, describes metabolomic spectroscopic technologies for the rapid, accurate characterization of biological systems. Secondly, **Paul Sturman,** PhD, describes mechanisms of biofilm formation and what makes them so difficult to eliminate within industrial and medical settings. Yet again, *PDA's 4th Annual Global Conference on Pharmaceutical Microbiology* will prove to be the only event to bring together established global experts in both fundamentals and practical aspects of microbiology to its delegates.

Improved economy, efficiency and expediency targets in the microbiology laboratory are goals for many of us and distinctly achievable by adopting novel/rapid microbial testing technologies coupled with the incorporation of "lean lab" concepts. This year's conference is replete with presentations describing rapid technologies, such as the integrated microarray platform technology for expedient automated microbial identification by **Peter Ball** and a new qPCR platform with outstanding speed and sensitivity for the quantitative detection of microorganisms by **Bjorn Breth,** PhD. **John Lohr,** PhD, and **Michael Miller,** PhD, will both be delivering presentations on currently available rapid technologies, return on investment and providing guidance on how to successfully implement and validate. These talks are complemented by session topics covering the limit of detection of microbiological tests and new method qualifications using alternative statistical tests for equivalency and non-inferiority.

The need for change in microbiological analysis is no more acute than in the testing of in-process samples, and finished product for Mycoplasma

The perfect complement to new technologies is a fitter and faster (lean) laboratory, and manufacturing environment with process flows that are specifically engineered toward efficiency. To this end, **Amy McDaniel** will speak about the incorporation of lean concepts in the QC laboratory. Lean principles and cost efficiency do go hand-in-glove with enhanced product quality realized in manufacturing process by the adoption of Quality by Design (QbD) principals and the implementation of Process Analytical Technology (PAT). A regulatory view of QbD in microbiological terms and potential benefits to industry from implementation will be described by the U.S. FDA's **Stephen Langille,** PhD. The ultimate goal of marrying QbD with PAT is the "real time" release of drug products. I will then answer the question, "can novel rapid microbiological technologies coupled with the principals of ICH Q8, Q9 and Q10 enable parametric release for aseptically filled drug products?" Several presentations cover sterile manufacture: new and novel sterilization methods by **Ash Khorzad,** and industry best practices developed to cope with some of the acute challenges faced in the sterilization of drug products by **Jeanne Moldenhauer** and **Dave Adams.**

Relocating microbiology analytics to the manufacturing environment is a necessity for swift evaluation and commensurate response to improve the microbiological critical quality attributes of products. **Renee Blosser** will moderate a session devoted to the environmental monitoring of a diversity of manufacturing environments presented by global experts: **Jim Akers,** PhD, and **Scott Sutton,** PhD, with environmental trend analysis given by **Austin Kuo.** Control of environmental microorganisms and contaminants is of equal importance; a comprehensive review of gowning and protective gear strategies for aseptic manufacturing will be delivered by **Art Vellutato.** This is followed by a regulatory discussion on objectionable organisms associated with non-sterile operations and a regulatory viewpoint on therapeutic biological proteins by the FDA's **Dennis Guilfoyle** and **Anastasia Lolas,** respectively. One of the possible consequences of inadequate environmental or manufacturing control can be a sterility test failure posing one of the greatest investigative

challenges a microbiologist might face. **Ken Muhvich** will speak on this topic, and provide an overview of investigative trends. If you are ever involved in a sterility test failure, this presentation will prove invaluable!

The need for change in microbiological analysis is no more acute than in the testing of in-process samples, and finished product for Mycoplasma. **Anthony Cundell,** PhD, will present on the new USP Chapter <63> on Mycoplasma Testing. **John Duguid** will detail an elegant application of risk analysis permitting evaluation of the applicability of twenty commercial Mycoplasma tests applied for lot release.

Endotoxin testing is one of the many analyses which is being relocated from the laboratory to the manufacturing floor. **Ron Berzofsky,** PhD, will provide an overview of the history of this technology and **Mike Dawson,** PhD, will discuss test selection, validation and application in a session on endotoxin testing. Yet another international expert, **Kevin Williams,** concludes this session with two case histories on the in-process testing of water for injection, intermediates and finished product on the manufacturing floor.

Finally, there are three truly unique sessions each essential development opportunities for the pharmaceutical microbiologist. A session called "Pharmaceutical Microbiology 'Urban Myths'" will answer the question of how much of common wisdom is actually based on fact in the pharmaceutical industry. Filtration, water systems and environmental monitoring will be explored with an eye to determining whether "best practice" is indeed "good science." The penultimate session is dedicated to global compendial updates. As a finale, the "Ask The Experts Roundtable Discussion" provides you, the delegate, with the opportunity to quiz representatives from international regulatory agencies, pharmacopoeias and industry experts. The panel of experts is outstanding.

Clearly, this year's conference remains the premiere event for microbiologists. This is one stimulus to your company's drive for increased quality, economy, efficiency and expediency which should not be missed!

PDA's Who's Who

Dave Adams, Engineering Specialist, Baxter

Jim Akers, PhD, President, Akers Kennedy & Associates

Peter Ball, PhD, Technical Marketing Director, Marketing, Pall

Ron Berzofsky, PhD, General Manager, LAL Division, Wako Chemicals USA

Renee Blosser, Microbiologist, CVM, U.S. FDA

Bjorn Breth, PhD, Product Scientist, Greiner Bio-One

Anthony Cundell, PhD, Director, Pharmaceutical Science, Schering-Plough

Mike Dawson, PhD, Engineer, Regulatory, Associates of Cape Cod

John Duguid, Staff Scientist II, Manufacturing Technical Services, Genzyme

Roy Goodacre, PhD, Professor, Biological Chemistry, School of Chemistry and Manchester Interdisciplinary Biocentre, University of Manchester

Dennis Guilfoyle, Pharmaceutical Microbiologist, Office of Regulatory Affairs, U.S. FDA

John Lohr, PhD, Associate Director, Sterility and Endotoxin, Microbiology, Alcon Research

Amy McDaniel, QC Manager, Microbial Science & Technology, Wyeth

Mike Miller, PhD, President, Microbiology Consultants

Jeanne Moldenhauer, Vice President, Excellent Pharma Consulting

Ken Muhvich, PhD, Principal Consultant, Regulatory Compliance, Micro-Reliance

Ash Khorzad, Manager, Research, Baxter

Austin Kuo, Environmental Monitoring Team Leader, Eli Lilly

Stephen Langille, PhD, Senior Microbiology Reviewer, Officer of Pharmaceutical Science, CDER, U.S. FDA

Anastasia Lolas, Microbiologist, CDER, U.S. FDA

Paul Sturman, PhD, Coordinator, Industrial Development, Montana State University

Scott Sutton, PhD, Senior Director, Microbiology Services, Vectech

Edward Tidswell, PhD, Sr. Director, Sterility Assurance, Baxter

Art Vellutato, Vice President, Technical Support Operations, Veltek Associates

Kevin Williams, Microbiologist, Eli Lilly

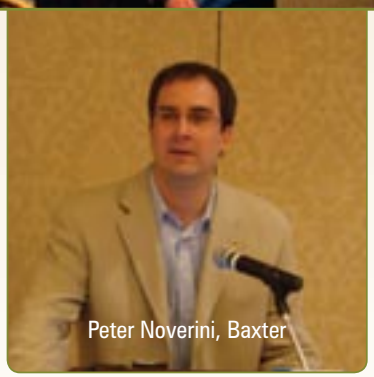
Faces and Places

Workshop on FDA's New Guidance on Process Validation

October 26-27, Bethesda, Md.

Susanne Rommel, Bayer; Hal Baseman, ValSource; Gretchen Allison, Pfizer; Rodney Thompson, BioPharm Process Associates; Christopher Smalley, Wyeth; Kelly Tunney, Merck

Rodney Thompson, BioPharm Process Associates



Peter Noverini, Baxter

Susanne Rommel, Bayer

Conducting Effective Training With a Shrinking Budget

Anita Pane Whiteford, PhD, Pennsylvania College of Technology

Training and development are one of the most critical areas to the success of an organization and their workforce. In this tight economy, training typically is one of the departments that becomes the victim of the organization's cost cutting containment measures. When training budgets become tightly squeezed, organizations have difficult decisions to make in the selection process of which departments should be downsized or eliminated, and which departments stay intact. In a regulatory environment, keeping the training function in full operation is imperative to the organization in the respect of satisfying not only the consumer but also the United States Food and Drug Administration (U.S. FDA).

Importance of Effective Training in A Challenging Economy

In a regulatory environment, every aspect of an employee's job has some significant impact on the lives of human beings. This impact could entail the manufacturing of pharmaceutical drugs, medical equipment and/or medical supplies. Over the last two decades, globalization has had a significant toll on our country and workforce. Competition in workforce labor skills is one such area of significance where higher skilled labor and lower costs can be utilized overseas. The dilemma with our workforce is the lack of higher skills, knowledge and inability to work for low wages. Therefore, leaders and senior managers must be cognizant of continually providing training to their workforce, and to the effectiveness of the training. In order to survive in the current complex and challenging economy, leaders must make critical decisions to financially support learning and development of their human capital. It will be this human capital that truly is the key to the organization's growth and future successes when the economy begins to spin back in a positive direction. CEOs and senior leadership must be creative when making those critical decisions. In a regulatory environment such as pharmaceuticals, training and development is a necessary ingredient for survival, and eliminating training positions would not be in the best interests of the organization.

Doing More with Less

In these turbulent times, organizations are watching budgets and pulling purse strings tighter to conserve capital in every way. One obvious way of controlling costs are limiting the number of people sent externally for training. This has been a popular trend with companies due to the current economic conditions. The disadvantage, of course, to this cost controlled measure is that people lose the networking opportunities with other trainers in the same industry sector, and are not as exposed to the FDA. The question raised by leaders and training professionals is: how can we continue training and development and invest in our human capital with spending less money? There are a number of avenues to explore in response to this question. Internal as well as external avenues will be identified and discussed. These avenues are successful effective delivery methods for training the workforce, and considered (low-cost if at all) no cost. In regards to this discussion of cost, there must be a clarification among the meaning of high cost training versus low cost training. High cost training typically involves sending employees outside to training events or having a trainer come on-site to deliver training. The costs absorbed would be for travel, trainer's time and expertise, and logistics. Low cost training is the target of this article where costs are basic and minimal.

Internal Subject Matter Expert Training Opportunities

Organizations can be thrifty with training budgets by utilizing their human capital to help with the responsibility of training. Internally, organizations can conduct on-the-job training; train the trainer programs; cross-training; coaching; in-house training and training through corporate universities. These internal training options are widely applied; however, there may be additional options that organizations utilize.

On-the-job training: Hands on learning for the employee utilizing the required equipment and resources as they are learning the job. This method of training would be the most effective learning environment for an employee due to the fact that the employee is demonstrating transfer of learning simultaneously as they are gaining the knowledge and skill through instruction.

Train the trainer programs: Due to expensive price tags on training events, organizations will send one or two employees to be trained on a particular topic. The employees will return back to the organization and be expected to train other employees that need the same particular skill or knowledge. The employees are labeled as the trainer with subject matter expertise for the particular topic in the organization, and will train other employees in the future.

Cross-training: Training that covers several tasks within a department or office. Employees in a particular department will master their own tasks of responsibility, and the tasks of their co-workers in the event that extra help may be needed and different areas require coverage. Cross-training can typically be accomplished internally with the more senior employees being the trainers. Cross-training is appropriate when turnover is high, and headcount cannot be filled immediately due to budget cuts.

Coaching: Method of instruction or training an employee or group of employees with the desired outcome to obtain a certain level of knowledge or skills. Coaching may consist of seminars, workshops or supervised work. Coaching may be either on a management to employee level or peer-to-peer level.

In-house training or brown bag lunches: In-house training is an excellent way to provide training to the majority of the workforce without a hefty price tag. Facilitators for in-house training must be the subject matter expert of the training topic. The majority of organizations identify employees as candidates who have demonstrated outstanding knowledge and skill on the training topic through work tasks and competency levels. Brown-bag lunches are a good way to recruit individuals to training events where they can come voluntarily for one hour during lunch time, and bring their lunch to eat while participating in the training.

Corporate universities: As a result of past and present economic turmoil, corporate universities have become increasingly popular the last few years. Corporate universities offer employees a variety of opportunities for personal development that foster a change toward organizational learning and knowledge. A few advantages for corporate universities are employee retention, organize training with course schedules and catalogs, high return on investment for learning and remain competitive in the global market. Corporate universities consist of many in-house trainings where employees are the facilitators.

Learning management system (LMS): LMS may be linked under corporate universities and widely used in regulatory environments. LMS is a computer software program to deliver, track and manage training. A number of courses maybe housed in the LMS with easy access by the employee to register for the courses, schedule the courses and take the courses. The type of training an LMS can provide is synchronous (self-instruction), asynchronous (collaboration with others), blended and classroom based training.

External Subject Matter Expert Training Opportunities

Externally, many different low-cost training methods can be utilized from the employee's home if they telecommute or if they are on-site at the organization. Elimination of travel to training sites saves organizations time and expense. Externally, organizations can seek webinars, podcasts, e-learning events, videoconferencing and state funded training grants through workforce investment boards. In addition, organizations may be able to unite with other organizations in the same pharmaceutical industry seeking a particular training to obtain a group training discount from the vendor due to high demand of the training. If an organization is global, large numbers of employees from various locations will be able to attend the training at similar times, or view a recorded version of the training at a later time.

Webinars: Meetings and presentations conducted via the internet where the presenter is on-line presenting the information, and the participants are sitting at their desks or conference room receiving the training. During webinars, participants are given the chance to ask

the trainer questions through the phone line that is required for operation of the webinar. The trainer also takes minipolls at various points during the training getting participant feedback on issues. Many training based organizations offer free webinars to industry-based organizations.

Podcasts: A series of digital audio or video media files that are available for download through websites. Podcasts are great tools to have for the workforce to attend at various times due to shift work or difficult availability.

E-Learning: Becoming a widely popular training delivery method in organizations where participants take courses electronically via the computer. Time and resources may be demanding to set up the e-learning courses initially; however, the organization saves costs on facilitator and logistical needs long-term.

Videoconferencing: This training method allows for multiple sites within organizations to connect together at the same time to participate in training events, meetings or presentations. The training is conducted through video and audio transmissions simultaneously. Videoconferencing is extremely helpful in organizations with global sites that also need regulatory training.

State Funded Training Grants: Organizations may be able to qualify for free grant money specifically for training and development of their workforce through the state they reside. Organizations can contact their local workforce investment board to inquire about free grant money for training. In addition, some industries have consortiums where free money may be available for organizations to train their workforce. Information on states' workforce investment boards can be found at www.dol.gov.

Choose Training Wisely

Many organizations are limited in the number of trainings they can offer their workforce per year, and the dollar amount of those trainings. Therein lies the question, how does an organization know which training is appropriate, effective and cost fitting for the workforce? First and foremost, the trainings selected must be in alignment with organizational strategic goals. Ineffective training occurs when management decides to conduct a particular training that has no significant ties to the necessity of operations, organizational goals or the workforce skill levels. Management selects the trainings because it "reads" well on paper. Management must ask themselves what the current skill deficit in the workforce, what direction the organization is going in, what value and impact the trainings must have on the organization and workforce, what the short term and long term strategic goals are of the organization and how the trainings align with this.

Organizations can seek answers to these questions by conducting a formal needs assessment. A formal needs assessment will require integration of employees, management, and other stakeholders

that would be involved in the training events to share their feedback regarding the value and impact of specific targeted trainings. Needs assessments take the form of interviews, observations, surveys, questionnaires and focus groups.

Conclusion

Organizations, especially if regulatory-based, must continue the operation of training and development in these hard-pressed economic times. As discussed in this article, there are a number of different ways organizations can take advantage to train their workforce in a low cost manner. The future of our workforce is in critical danger as a competitor in the survival of globalization. Regulatory-based organizations must take every measure possible to remain competitive with a highly skilled knowledge-based workforce.

About the Author:
Anita Whiteford, PhD, is a faculty member at the Pennsylvania College of Technology in the School of Business and Computer Technologies department. She is teaching in the discipline of human resources management. Previously, she worked in the pharmaceutical industry as a training professional. Whiteford serves as a member on the *PDA Letter* editorial committee, and can be contacted at apw1@pct.edu.

To learn more about the TRI course "An Introduction to Visual Inspection," which covers the fundamentals of visual inspection and their application to injectable products, visit www.pda.org/visualinspectioncourse

TRI's QRM, Process Validation Courses Brought to PDA Israel Chapter

Karen Ginsbury, PCI Pharmaceutical Consulting; Raphy Bar, BR Consulting; Bob Dana, PDA

PDA TRI staff and TRI instructor **Hal Baseman,** Principal and COO, ValSource, visited Israel in July to provide expert professional training on Quality Risk Management and Process Validation. Hal was one of the brains behind *PDA Technical Report No. 44, Quality Risk Management for Aseptic Processes,* and one of the coordinator's of PDA's comments to the U.S. FDA on the 2008 draft guidance, *Process Validation: General Principals and Practices.*

The PDA Israel Chapter hosted the courses and provided additional course faculty. Chapter President **Raphy Bar,** Consultant, BR Consulting, provided a detailed but concise overview of the use of design of experiment in process validation. **Karen Ginsbury,** President, PCI Pharmaceutical Consulting, addressed statistics in Process Validation and some aspects of quality risk management. The coverage of these two statistical topics nicely reflected the approach of the new draft guidance, which strongly advocates the use of statistical tools and design.

Raphy Bar, BR Consulting

Both were two-day courses and included lively workshops with highly interactive audience participation. Hal divided the classes into "smart" vs. "beautiful," and the argument is ongoing as to which group was which, particularly since all outcomes were brilliant.

Risk management participants took away practical examples of Ishikawa (fishbone) diagrams and their application in developing a preliminary hazard analysis. They had a brainstorming session on possible failure modes and for assigned levels of severity, likelihood of occurrence, likelihood of detection, as well as additional controls that could be used to mitigate the risks that were identified and to lower the risk priority number. This exercise was repeated twice: first for a coffee maker, and then for a pharmaceutical process.

Attendees listened intently at PDA's TRI Israel Chapter course series

Participants in the process validation course were given an overview of current validation practices and contributed to a lively discussion of the aforementioned draft FDA guidance document on process validation. Possible modes of preparing for implementation of the guidance and for the life cycle process validation were brainstormed, as well as approaches to ongoing verification, particularly for legacy products.

Hal outdid himself, and may have set a new record for TRI faculty for running a course four consecutive days without a break. However, since there was unanimous agreement that he is wanted back in Israel next year, the Chapter has promised to allow him one day off for sight-seeing and relaxation between the courses. PDA TRI leader **Bob Dana** was there behind the scenes, facilitating arrangements and providing additional support in the workshop sessions.

(l-r) Karen Ginsbury, PCI Pharmaceutical Consulting; Hal Baseman, ValSource; Raphy Bar, BR Consulting

It is the hope of all concerned that this might be the first of an annual PDA Israel Chapter TRI training course series, and if so that 2010's courses will be as successful and as much appreciated as those of 2009.

First Public Discussion of EFPIA Mock QbD Submission at PDA Workshop

An interview with EFPIA representatives Graham Cook, Robert Schnepf and Brian Withers by Volker Eck

To gain a better understanding of the necessary information to support a "Quality by Design" (QbD) approach, the European Federation of Pharmaceutical Industries and Associations (EFPIA) is working on discussion papers about how to generate QbD data for presentation in the drug substance (S2) and drug product (P2) portions of the Common Technical Document (CTD) when submitting a new drug application. The most recent papers will address parenterals and APIs, and include mock submissions to help companies prepare their own filings. For the first time, representatives of the teams that put together these discussion papers and the Mock S2 and P2 filings will publicly discuss the project at the *PDA Workshop: Quality by Design—Putting Principles into Practice*, September 22-23 in Frankfurt, Germany. **Graham Cook**, PhD, Wyeth and **Brian Withers**, PhD, Abbott, will discuss the EFPIA project during the afternoon "coffee table" discussions on Tuesday, September 22. To learn more, visit www.pda.org/qbd2009.

PDA's **Volker Eck**, PhD, spoke with Graham and Brian about their participation in the upcoming workshop in an interview with Graham and Brian. **Robert Schnepf,** PhD, Merck, who serves on the EFPIA group, also participated in the interview to talk about the discussion papers. The following is the interview in Q&A format. The initials VE, GC, RS, and BW are used for Volker, Graham, Robert, and Brian's names, respectively.

VE: Why is EFPIA doing the mock documents?

BW: EFPIA compiled the first "Examplain" Mock P2 discussion paper, which gave the pharma community (industry and regulators) the ability to see a case study illustrating some concepts described in the ICH Q8 (R1), Q9 and Q10 guidance documents. The EFPIA "Examplain" Mock P2 paper described a solid oral product and was intended as a discussion paper for some Quality by Design concepts including proposals for flexible regulatory approaches. It was felt that injectables would benefit from being discussed in a separate paper. Initially, only a terminally sterilized formulation was targeted, but it was clear that a lyophilized product was sufficiently different to warrant an independent document that would concentrate on this process, and its implications when QbD concepts were applied.

GC: The starting point for the Mock S2 documents was the recognition that ICH Q8 with its appendix was written to apply to drug products. Some companies were applying QbD principles to the development and manufacture of drug substances, and it was felt that there would be value in creating discussion documents that demonstrated some current industry thinking in this area. So EFPIA started the project and two teams were created, one covering a small molecule API synthesis, and another covering the development of a monoclonal antibody. As with the first Mock P2 discussion paper, the intent of these documents is to demonstrate to industry and regulatory authorities what the application of QbD principles to drug substance development and manufacture could look like, and what tools could be used. The mock documents, however, are not intended to be a complete S2 section, but rather to present enough information to provide a basis for understanding and help identify the opportunities that can be gained through the development of enhanced scientific understanding and sharing this knowledge.

BW: So to exemplify some potential QbD examples in the S2/P2 parts of CTD regulatory submissions, we ended up with four mocks: QbD principals applied to terminally sterilized and lyophilized injectable drug products, as well as to small molecule and monoclonal antibody drug substances.

Robert: The discussion papers do not detail the complete submission part of a hypothetical CTD, but touch on the most important conceptual cornerstones. They are aimed to give practical examples and stimulate discussion on those. To be most inclusive, the groups were put together to reflect the diversity in situations and potential solutions to the multitude of problems encountered during product development. To do so, experts from different functions from EFPIA member companies were asked to participate and share their thoughts, examples and experiences in applying QbD.

VE: How did you and the group work to compile the mock document?

BW: The purpose of these case studies is to provide some examples of how a S2 and P2 section, respectively, might look like for a parenteral product developed using an enhanced QbD approach to development as envisaged in Q8R. They are not intended to be all encompassing, and are not intended to represent the only way that development of a parenteral product can proceed, or be presented. They are intended to be used to stimulate thought and discussion of the possibilities that ICH Q8, 9 and 10 present for potential products. So, the first thing to do was to create a story of the development of a hypothetical product, and choose what process steps and unit operations would be best to illustrate such a QbD approach.

RS: It is true that some QbD approaches were already used in all companies, but not necessarily a concise and focused one. We used data made available from the companies participating that were anonymized for being published in the document. Although the data was original, the conclusions drawn might not be identical to the original

ones, as the discussions around it the data treatment and interpretation was a group exercise. We also included input from ad hoc subject matter experts if we felt the group didn't possess the necessary expertise in certain cases. At the end, we also plan to highlight benefits of the application of such an enhanced QbD approach. And, for example, suggest some areas where flexible regulatory approaches might be applied that would be safe and scientifically sound when it comes, for example, to process changes and their impact on the quality defined in the original submission.

GC: I like the "concept car" analogy that came from a member of the original Mock P2 team. You could compare the mock documents to a concept car that you might see at a motor show. It has the look and feel of the future model, but not necessarily all technological parts are fully developed or built to enable it to operate at full performance. Creating scientifically credible stories for the development of the hypothetical drug substances described in the mock documents is not easy, and so in many cases, the team members would base the sections they were writing on real examples from within their companies and change them to fit the story we were trying to tell. When the groups had to decide what process steps or unit operations should be discussed, the principal selection criteria was to show examples that could be used to illustrate ideas, the use of tools and perhaps provide a model for others. By doing so, the discussion papers can be useful to the industry and experts from authorities as a practical guide exemplifying some of the important questions and potential solutions to application of QbD principles. As you might imagine the process of developing the documents has required several face-to-face meetings of the team members. In these meetings, there has been intensive discussion about the interpretation of the QbD concepts and principles described in ICH Q8, 9 and 10, sharing of the various company's experiences, creativity in the application of science-and risk-based approaches to gain product and process understanding, and then describing such a study in the appropriate section of the CTD format submission.

VE: What did you learn by participating in this work?

RS: The whole exercise started 18 months ago. We just finished our final draft for review. During this whole period, the groups underwent a constant learning experience. It is quite a difficult task to transpose philosophical concepts into practical solutions, and during the discussions a lot of details popped up that needed to be addressed. Participating at these group discussions broadened my view on potential solutions and their impact. It challenged the way of traditional reasoning and decision making, and I learned that a variety of solutions were existing to the problem given. Given the fact that the group members did all this in addition to their daily work, that most if not all continued to contribute from the beginning, is evidence of their enthusiasm and dedication to this. It also is fair to state that who stayed, did so because they learned a lot from the others during the discussions we had.

GC: I can only echo this from my experience. The discussions and debates in the meetings are by far the most educational experiences by helping to broaden the understanding of what is meant by QbD, and also how to apply this to a given problem. It was always amazing to see how bringing experts from different areas together helped generate a good story for these hypothetical developments. This reinforces the benefits of breaking down barriers between different functions in real companies when developing and manufacturing products.

VE: What will users learn from the mock document?

BW: As I said before, the papers are to be used to stimulate discussion. They do not give a recipe or generic solutions. Once understood, they can be used as a starting point for thinking about applying QbD to real projects. As we have chosen common process steps and unit operations, a broad range of practical problems should be encompassed, but companies must take into account the particular circumstances of their projects and organizations if they are to be successful.

VE: What are the next steps?

BW: Certainly our participation at the PDA workshop and the feedback from delegates will help us to understand if we as a group have created something that stimulates discussion, and is also helpful for companies to follow an enhanced QbD approach to development. It is too early to give an estimate of when the four papers will be published, but the teams are working hard to finish the documents and make them available to EFPIA.

VE: What will you be sharing at the PDA QbD workshop?

GC: Included in the PDA meeting are some presentations on the Mock S2 and P2 projects, but, in addition, the workshop is set up to give the participants an experience close to the one all of us had in participating in the EFPIA mock groups. Delegates will have the chance to meet subject matter experts, to discuss the most burning problems and identify possible solutions through joint discussions. This certainly is not a crash course in enhanced QbD applications, but it is realistic to expect to leave the workshop with a better understanding on how to apply QbD. Also, the setting of the workshop with parallel coffee table discussions will enable participants to select topics and adjust their schedule to match their interests and needs. During the workshop, participants are encouraged to move from one table to another to join in the different discussions. This format will allow participants with different levels of expertise and experience to specifically address their individual problems, comments and questions concerning QbD in a variety of topics, both the general aspects, as well as very specific and focused issues. We are ready to share our experience and knowledge on QbD with the participants, and encourage them to discuss and challenge what we have put together.

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Learn About Sterility Assurance-Boosting Technologies, Practices

Sterilization Technology, Today and Tomorrow • Milan, Italy • November 17-18 • www.pda.org/sterilization2009

Klaus Haberer, PhD, Compliance, Advice and Services in Microbiology; Volker Eck, PhD, PDA

We are pleased to announce that PDA will be continuing its series of conferences *Sterilization Technology Today and Tomorrow: Building and Maintaining Sterility Assurance* in 2009. It is our intention to provide a platform for experts of industry and authorities to share their knowledge on sterility assurance with you, to help you save money and time spent. We are proud to present to you a panel of excellent speakers that will highlight the different aspects of sterility assurance from the perspectives of suppliers, users and the regulatory bodies.

The conference will give you the opportunity to explore industry best practices in application of sterilization methods and technologies from materials, components and finished pharmaceutical/biopharmaceutical products and medical devices. Established technologies will be reconsidered in the light of recent improvements, and new developments will be discussed in their potential for future use and production. The agenda will include sessions covering experience, positions and aims of international and EU representatives; thereby, highlighting the most advanced approaches to sterilization and sterility assurance.

Specific session topics include:

Sterility Assurance and Parametric Release

This session will review regulatory expectations for prerequisites to achieve approval for parametric release of medicinal goods. It will outline the preparatory steps to be taken to cover the critical aspects raised by the regulatory bodies during the review process. Companies who are granted permission for parametric will present their solutions and the benefits achieved.

Sterilization Processes—Regulatory Experiences

We are pleased to welcome for this session recognized speakers from regulatory bodies. They will give feedback from their broad experience in assessing, and inspecting manufacturing sites for sterile medicinal products. It is their intent to illustrate the most frequent observations and the underlying misinterpretations of guidances. The session will help industry gain better understanding of the expectations of regulatory bodies when it comes to sterility assurance in manufacturing.

Sterilization/Sanitation/Disinfection/Decontamination

Sterilization is the ultimate step in rendering an article or component free from microorganisms. However, other activities that reduce the number of living microorganisms, e.g., in the environment on equipment surfaces, in the process stream are integrated into sterility assurance concepts. This lecture will specifically address qualification and validation issues, as well as training aspects and built-in solutions. Participants will bring valid information home, as well as ideas they can adopt to their situation.

Risk Assessment/Risk Management

Quality risk management has become a very strong basic concept which is expected today to be applied to all manufacturing activities for medicinal products. In Europe, the ICH Q9 concept of risk assessment and risk management has been introduced into the GMP guidelines as Annex 20 to the EU GMP Guide. This lecture will review aspects and examples of performing a risk evaluation to gain systematic understanding about the measures necessary to achieve the expected sterility assurance level, and to strive for continuous improvements of the process.

How to Avoid Contaminant Ingress for Lyophilization Chambers

Lyophilization chambers for aseptically manufactured sterile products should be maintained as sterile compartments. Opening and closing the chamber for loading trays into the equipment are critical handling steps as the air flow pattern is distorted and contaminant ingress becomes a potential risk. This presentation discusses the use of a model to determine the level of risk, and to evaluate countermeasures. Their effect and efficiency will be illustrated using a case study.

Maintaining Sterility

Manufacture of sterile medicinal products should be accomplished by use of a comprehensive process and not just by relying on a sterilization process. There are many sources of potential contamination within a manufacturing process, and the environment it is performed in. One of them is personnel and tools brought into the manufacturing area. The facility layout and the equipment selected can have an impact as well. We are proud to announce the presentation of a state-of-the-art solution; a facility designed to contain built-in measures that support optimal sterility assurance for unit operations in addition to the sterilization step.

Ready to Use Stoppers

To reduce preparation and process times as well as other ancillary activities, ready-to-use stoppers are an option. This lecture will illustrate how such stoppers are manufactured and what validation activities have been performed to verify the sterile status of these primary packaging components.

Biological Indicators

Biological Indicators (BIs) are essential to verify the biological effectiveness of all sterilization procedures. While the lethal effect can be predicted to some extent from the physical characteristics of the sterilization process, the biological effect remains the ultimate goal. There are some options as to how and when BIs can be approved. This lecture will discuss the influence of sterilizing conditions on microorganisms, and derive solutions to select the best choice of

BI studies for a given situation. It also will give important background information to the practitioner.

Parametric/Real Time Release: A Regulator's View

The EMEA has recently published a position paper that extends the concept of parametric release beyond its application to terminally sterilized products and discusses the real-time release option that would be granted in a Quality by Design setting. It is not clear at this time, under which conditions the concept of Parametric Release might also be extended to aseptic processes. We are pleased to have a regulator with us, who is discussing what this would mean to the level of sterility assurance implemented for any manufacturing process and environment.

Ph. Eur./Harmonization Activities

It is important for the professionals in the field to be updated with the activities that are ongoing in the pharmacopoeia, and regulatory bodies that issue guidelines. Input is needed by the working parties to help developing the guidelines. The lecture will illustrate discussions and projects within the European Pharmacopoeia, and beyond with regards to monographs on sterilization techniques and sterility assurance.

We are convinced this program will help you to do your job better, and are looking forward to welcoming you and your colleagues in Milan in 2009

You will hear directly from the experts who wrote sterilization guidance documents regulators like **Tor Gråberg,** Chief Pharmaceutical Inspector, Medicinal Products Agency, and Chair-elect for the Pharmaceutical Inspection Co-operation Scheme (PIC/S), and industry speakers from leading companies in the health care and life sciences industry. If you want to learn more about this, visit www.pda.org/sterilization2009.

We are convinced this program will help you to do your job better, and are looking forward to welcoming you and your colleagues in Milan in 2009.

First Public Discussion of EFPIA Mock QbD Submission at PDA Workshop, continued from page 51

VE: How can the PDA QbD workshop help in that?

RS: Much too often the potential of applying QbD is not seen or underestimated. It might be considered too complicated, implying a big workload, costing time, resources as well as precious substance and without immediate benefit. This PDA workshop offers the opportunity to challenge all this preconceptions and to learn from the example of the EFPIA groups how much of this is true. As these groups represent a fair share of the various organizations within the pharmaceutical industry that are members to EFPIA, participants will be able to see how these aspects were addressed from different angles and solutions found matching these realities.

GC: I personally would like to invite the readers to come to this workshop. Everything has been designed to try to ensure that participants will leave satisfied and enriched by the experience, with their issues addressed and discussed with a variety of subject matter experts. The coffee table format chosen by the organizing committee will help to convey the spirit and experiences of the discussions we had in our EFPIA groups.

VE: Many thanks for this interview

[Editor's Note: In addition to the September workshop, extensive discussion of QbD and related issues is planned for the PDA/EMEA Conference on October 13-14 in Berlin. To learn more, visit www.pda.org/emea2009.]

About the Experts

Graham Cook's current position in Wyeth's Global Quality & Compliance organization is Senior Director, Process Knowledge/Quality by Design. He is responsible for leading Wyeth's Quality by Design efforts for all business units (Pharmaceuticals, Biotechnology, Vaccines and Consumer Healthcare) in Europe, Asia-Pacific and Latin America. He has been involved in Wyeth's global QbD submissions and the QbD/PAT Variations submitted as part of the EMEA Worksharing pilot. He holds the Wyeth vote in the ASTM International E55 committee, which is developing consensus standards for QbD/PAT in pharmaceutical manufacturing. Graham is active in several EFPIA QbD/PAT initiatives, coordinating the development of "Mock S2" discussion documents illustrating the application of QbD principles to the development of small molecule and biotechnology drug substances, involved in the organization of the EFPIA-EMEA PAT team workshop in Ireland in 2008.

Robert Schnepf joined Merck in Germany in 2005. Currently, he is head of the group that is responsible for drug product formulation and process development of New Biological Entities (NBE's). In this role, he has been involved in internal efforts to implement QbD in drug product process and formulation development. Robert is active in the EFPIA QbD/PAT initiative to develop a "Mock P2" discussion document that illustrates the application of QbD principles to the development of NBEs and New Chemical Entities (NCEs).

Brian Withers currently serves as Abbott's Director of Chemistry, Manufacturing and Controls (CMC) regulatory with particular responsibility for Biologics. He is currently Co-Chair of EFPIA Product Development and CMC ad hoc group. He acted as expert on ICH Expert Working Group for Q8R.

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