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PDA Letter

April 2010

Volume XLVI • Issue #4

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In This Issue:

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Pharma's Reaction to Health Care Bill Mixed

Walter Morris, PDA

[Editor's Note: We have decided to delay this issue's features for an analysis of industry's reaction to the breaking news regarding the passage of comprehensive health care reform by the U.S. House of Representatives. We will publish a feature article on ASTM E2500 by Peter Watler, Hyde Engineering & Consulting, in a future issue.**]**

On Monday, March 22, it appeared that comprehensive reform to the way Americans receive health care will become a reality following the U.S. House of Representatives approval of reconciliation legislation that incorporates much of a bill approved by the U.S. Senate on Christmas Eve. The White House intends to sign the bill on Tuesday, March 23, and the Senate must approve minor changes.

Reaction to the landmark legislation came swiftly from the three major trade groups representing the drug industry in the United States. Both the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Generic Pharmaceutical Association (GPhA) issued statements Sunday night following the historic vote. The Biotechnology Industry Organization (BIO) issued a statement the following day.

PhRMA was generally supportive of the reform effort throughout the process, and this was reflected in their statement:

"We continue to believe that comprehensive health care reform will benefit patients and the future of America," the statement began. "That's why we have been involved in this important public policy debate for more than a year and why we support action by the House to approve the Senate-passed bill along with the amendments found in the reconciliation legislation."

PhRMA hinted that costs associated with the legislation that its members might have to bear could impact an already shrinking workforce in the United States. "Our commitment to help pay for health care reform will require all of our companies to make some difficult choices moving forward—on top of already losing more than 150,000 jobs since 2007 because of the recession and other economic factors."

The trade group indicated that more work needs to be done to overhaul the way health care is delivered and paid for in the United States. "But throughout this long process, we have been guided by a belief that all Americans should have access to high-quality, affordable health care coverage and services. This legislation, while not perfect, is a step in that direction."

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Please consider joining the Q-IWG for the Europe region training, the first of a series of three worldwide workshops, to be held in Tallinn, Estonia, 2-4 June.

I hope to see you there.
With very best regards,

Jean-Louis Robert
Rapporteur of the ICH Q-IWG & Chairman of the Faculty

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Cover art:
On Tuesday, March 23, the White House signed into law a Health Care Reform Bill. The drug industry, for the most part, supports the bill.

Coming Next Issue:
Manufacturing Excellence — Reports from the 2010 Annual Meeting

PDA Europe Parenterals Conference 2010

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Call for Papers & Posters

PDA is inviting abstracts for "Parenterals 2010" from interested members and colleagues in the pharma, biopharma, equipment, regulatory, academic and technology fields. Abstracts should focus on the following or related aspects of the parenteral business:

1. Production environments and their control, including environmental monitoring; cleaning, sanitization, sterilization; aseptic connections and transfers; gowning
2. Components & costs of quality including packaging, serialization, tolerance for defects, glass breakage, ready-to-use and ready-to-sterilize
3. Manufacturing including total process control, high speed automation, in-line testing, knowledge management, continual improvement, single-use components
4. Innovative manufacturing facilities including production planning (push/pull, flexibility), dedicated, single & multipurpose facilities
5. Isolators and RABS, and their impact on current industry trends
6. Impact of recent regulatory guidances including variations; ICH Q8, Q9 & Q10 and impact on knowledge management; FDA guidances; PIC/S Annex 1 interpretation; dedicated facilities; inspection trends
7. Cost reduction and efficient management in parenteral operations
8. Other topics relating to parenterals

All abstracts submitted before 16 April 2010 will be reviewed by the Program Committee for acceptance. Upon review by the Program Committee, the PDA will advise each submitter of the status of the paper for presentation in writing after 22 May and before 1 June 2010. Case studies are particularly desired. Commercial abstracts for papers or posters will not be considered.

Please include the following information. Submissions received without full information will not be considered.

- **Be submitted in MS Word format in English, max. 300 words**
- **Presentation length of approximately 30 minutes**
- **Title of presentation**
- **Presenter**
- **Presenter's biography (approx. 100 words)**
- **Additional authors**
- **Full mailing address**
- **Phone and Fax number**
- **Fax number**
- **E-mail address**
- **Key objectives of your topic**
- **Clear descriptions of the topic(s) to be covered and relationship to "Parenterals"**

PDA policy provides one complimentary conference registration to each accepted presenter. If more than one presenter, additional presenters are subject to appropriate registration fees. PDA is a not-for-profit membership association, and has limited resources to cover travel costs. Industry presenters are responsible for their own travel and lodging. Invited regulator/health authority speakers will be reimbursed for travel costs.

Poster Session: Poster abstracts should be clearly identified as 'Poster Session' and follow the same content guidelines as above. Poster abstracts can be submitted anytime until 30 September. You will be notified of acceptance within 2 weeks of submission. Abstracts not accepted for podium presentations may be invited for poster sessions. Poster session presenters are subject to applicable conference registration fees.

Please send your abstract and the required information to Ailyn Kandora (PDA Europe) at kandora@pda.org.
If you have any questions, please do not hesitate to contact us.

Contact PDA Europe:
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Event & Program Manager
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Attention Exhibitors

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Deadlines	Paper abstracts for presentation: 16 April 2010 Poster abstracts: 30 September 2010

Editor's Message

Stopping the Presses for Health Care Reform

Rarely do we at the *PDA Letter* get an opportunity to cover a breaking news story and one as monumental as health care reform in the United States. But due to the confluence of unrelated events, we chose to take a pause from our regularly scheduled content and provide a "breaking news" story on this issue's cover. It is not often that events in Washington hit so close to home as the health care bill, but as you can read in the statements issued by PhRMA, GPhA and BIO, this legislation will be mean a great deal to the pharmaceutical industry. And I think we all can agree, whether you are a Republican, Democrat, Libertarian, liberal or conservative, this bill is a paradigm-changer.

We are interested in knowing your thoughts on the issue, and provided an email address in the cover story for you to use. Maybe you think we should not have even bothered covering the comments of the three major trade groups, and that is a fair assessment that we'd like to know also. However, after reading the statements carefully over the last several days, I am confident in my belief that they are extremely insightful, brief as they are. It is clear from all three of the trade groups that the legislation is the start to changing health care in the United States, not the end. For instance, is the public option truly dead, or will it be back in future sessions? Will the opponents of the legislation successfully defeat in court provisions requiring individuals to purchase insurance? For political junkies, this bill promises to provide drama for years to come. For the rest of us, all we can do is see where the chips fall over time before we can decide if the reforms were beneficial or not.

Until then, we plan to return to our normal schedule in the May issue with articles from the 2010 PDA Annual Meeting. Speaking of that conference, I am happy to report that three members of the *PDA Letter* Editorial Committee—**Karen Ginsbury**, **Hal Baseman** and **Sandra Zoghbi-Gay**—were at the conference and took time to gather with me briefly following the longest day of sessions. I thank them for extending their day a little longer and can assure all readers that this current group of editorial volunteers is smart, active and dedicated. I look forward to working with them!

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Ten Years and Counting!

Janny Chua has been at PDA for ten years and is already looking ahead to her twentieth anniversary

Responsible for managing PDA's publications with duties covering day-to-day maintenance of the online PDA bookstore, publication orders, shipment, inventory, customer service and sales of the books/publications, Product Operations Manager **Janny Chua** has been with PDA for more than ten years.

When asked why she has stayed so long at PDA, Janny said it was because she is able to enhance her work, interpersonal and communication skills.

On top of her long-service to PDA, Janny has had 20 years of merchandising experience involving working with various stakeholders including buyers and designers. Janny said that her experience has helped her to meet the various challenges at PDA throughout the years.

"I am proud to be a long-serving member of the PDA family to continue my services to our customers and meeting challenges."

Janny said that she was "proud" to be a long serving member of such a highly respected and dynamic not-for-profit organization such as PDA to serve the pharmaceutical and biopharmaceutical industry.

"I have been with PDA for more than ten years since joining in November 1999. Into 2010, I look forward to enjoying another ten remarkable and rewarding years with PDA—making it a delightful 20 years."

Science & Technology *Snapshot*

Read the Journal Online in "Full Text" View and Make PowerPoint Slides

Walter Morris, PDA

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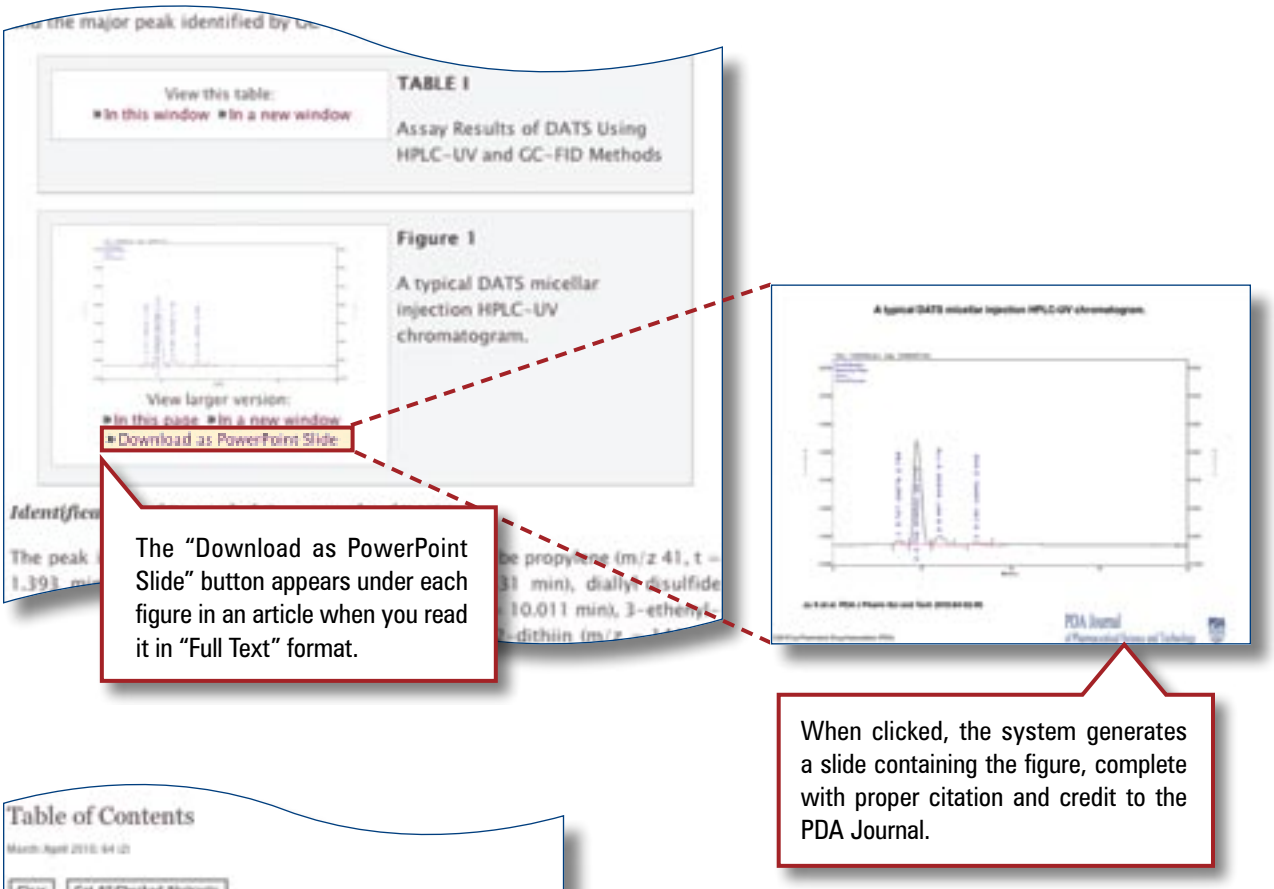

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Journal *Preview*

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Did you know you can receive the *PDA Journal's* Table of Contents by email and through RSS? Just go to journal.pda.org to sign up for these features and never miss an issue.

The March/April issue is available and includes an editorial by Associate Editor Kurt Brorson, PhD, U.S. FDA, entitled "PAT and the Future of Biotechnology." Ed Tidswell, Marc-Oliver Wright and Jim Rockwell contribute a commentary on reducing hospital-acquired infection deriving from intravenous bags. In addition, the issue includes six Research articles and three Technology Application articles.

The March/April Journal Table of Contents:

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"Visualization Techniques for Assessing Design Factors That Affect the Interaction between Pharmaceutical Vials and Stoppers" – Philippe Lam and Al Stern

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In *Print*

Perspective on Cleaning Validation and Revalidation

The following are excerpts from the PDA/DHI book, Cleaning Validation Practical Compliance Solutions for Pharmaceutical Manufacturing, *Vol. 2, by Destin LeBlanc. References have been removed from this excerpt but can be found in the book.*

Do Three Verifications Make A Validation?

The traditional approach to validation, including cleaning validation, is to perform a minimum of three validation runs. Of course, there is no statistical justification for three runs being acceptable. It is just something that pharmaceutical manufacturers and regulatory authorities have agreed on. In some regulatory documents (for example, PIC/S PI 006-03) it is written as a minimum of three runs. Based on previous communications from the FDA and the new FDA draft process validation guidance, the requirement for three validation runs is being replaced, probably by a statement that the manufacturer should decide on the required number of validation runs. Because of this, some manufacturers are changing their high level documents to read something like "three validation runs or a different number if appropriate." That "different number" may be more than three or less than three.

Verification protocols are protocols for one-off (unique or one time) cleaning events. Most companies would validate a cleaning process if that option were practical. However, for cleaning for clinical trial materials or for cleaning after deviations (such as exceeding the dirty hold time), a cleaning verification is appropriate. Some companies have chosen to treat verification runs such that if three verifications are done for the same product, the same equipment and the same cleaning process, then the cleaning process can be considered as validated (for that product and for that equipment). When this has been done, it is usually the practice that this be allowed (permitted) in the high level cleaning validation document for that company. Furthermore, when it is done, there usually is a validation protocol written at the same time the initial cleaning verification protocol is written to cover that possibility. Note that in this case, the three verification protocols may or may not be performed, so there usually should be some kind of time limit for completion of the three verification protocols. If not completed on a timely basis, then the "umbrella" validation protocol should be closed out.

All of this is preliminary to getting to my main point, which is whether this practice is justified. Like a good consultant, my answer is "It depends." If the three verification protocols are runs *without any other support data*, then my opinion *now* is that it is not appropriate to consider the cleaning process validated. This is a change in my opinion. What has caused me to change my opinion is that in my training seminars on

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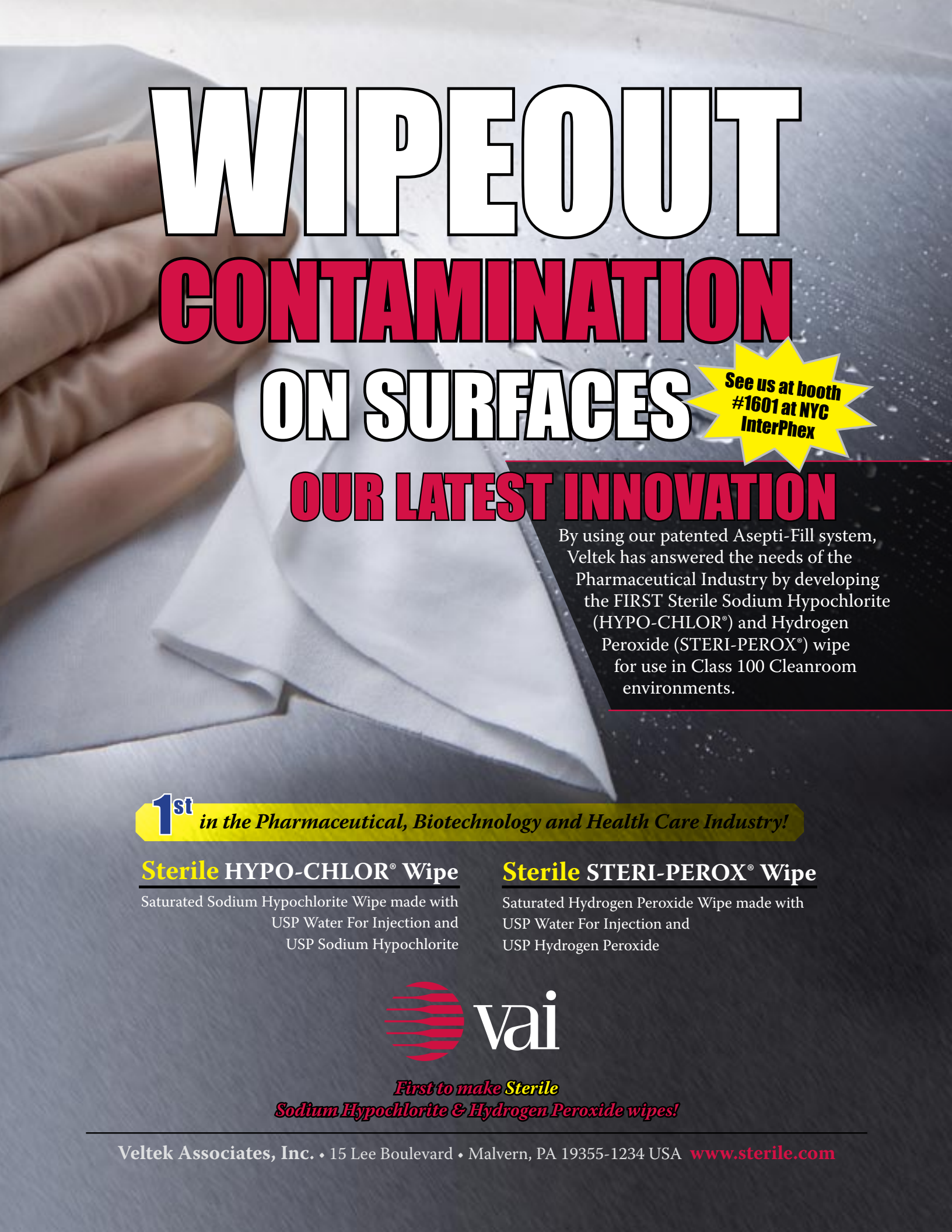
Open Journal Articles in "Full Text" View to make PowerPoint Slides, continued from page 8

The "Full Text" view has additional features that make it a good choice for reading articles online. For instance, there are special navigation buttons for the articles that allow you to quickly jump to different sections of the article.

References in the "Full View" are hot linked so you can jump to them or an abstract. PDA participates in HighWire Press's (our Journal host) "Toll Free Linking" for references, which allows you to obtain for free any article referenced in our Journal and hosted by a participating HighWire-hosted journal.

Another useful tool allows you to expand the "Full View" so it extends across the three page grid used for our website, allowing you to see more of an article on their screen at a time.



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Perspective on Cleaning Validation and Revalidation, continued from page 9

cleaning validation, I usually emphasize that it is not just the three validation runs that demonstrate consistency of the cleaning process. It is also all the prevalidation work (including design, lab studies, and scale-up studies) that helps support any claim about the consistency of the cleaning process. (Although not specifically related to this discussion, all work following the three validation runs also supports any claim of consistency.) Therefore, it is probably not appropriate to state that three verification runs (absent any pre-verification or other supporting studies) is a clear demonstration of consistency. For that reason, my opinion now is that three verification runs alone *do not* constitute validation. This consideration of process design and development is consistent with the FDA's proposed definition of "validation" in its new draft process validation guidance.

A key word in that last statement is "alone." It is not likely that extensive pre-verification studies would be done for a cleaning process that might be used only once. There may be limited studies, but remember that in a verification mode, if a failure occurs, then it is perfectly okay to clean again and retest until the acceptance criteria are met. Certainly recleaning and retesting are not a preferred mode. I would generally prefer to over design the cleaning process in a verification mode such that I met the acceptance criteria after the first cleaning event. However, this is clearly a situational decision.

If I do not have extensive support data on that cleaning process on that product and on that equipment, another possibility is to leverage data on related cleaning processes. For example, if I were in biotech manufacture and had successful cleaning validations on a variety of proteins using a certain cleaning process, I might leverage that data and use that to support the contention that three verification runs on a new (but similar) protein using the same cleaning process and similar equipment would constitute successful cleaning validation. Another situation might be in tablet manufacture. I believe it is generally true in tablet manufacture that it is the difficulty of cleaning of the excipients that determines the difficulty of cleaning of the final formulation. If that is the case, then successful validation of a variety of formulations might be used to leverage the contention that a new, but *similar* formulation, is validated based on three verification runs. If this is done, then this should be something that is allowed in the manufacturer's high level documents. This approach of using data on sufficiently similar processes is consistent with provisions of the FDA's new draft process validation guidance.

The purpose of this chapter is not to specify how to handle such verification runs, but rather to discuss issues relevant to how three verification runs might be considered as successful validation.

The above chapter is based on a *Cleaning Memo* originally published in August 2008.

What's Happening To Revalidation?

In the FDA draft process validation guidance the term "revalidation" is no longer used. What's behind this move? And will it apply to cleaning validation?

The latter question is probably easier to consider. Cleaning is a just another manufacturing process, and the principles of process validation certainly apply to validation of a cleaning process. The first question is the more interesting one, and the answers provided below are my best guess as to the rationale for the change. However, if you have kept up to date with the FDA's thinking for the last five years, the rationale is clearer.

First, "revalidation" for cleaning processes has meant one of several things. One is a yearly confirmatory protocol, usually a single run. This has been more common on fully manual cleaning processes (as opposed to fully automated cleaning processes) because of the concern about control and variability with manual cleaning processes. A second is a yearly review of all relevant data for a given cleaning process to document that the cleaning process is still in a "state of control." Relevant data may include routine monitoring data, change control data, deviations, training records, and quality records for products. A third use of revalidation is a validation protocol on a significant change in the cleaning process. It is perhaps this last use of revalidation that is of most concern. When I make a significant change in the cleaning process and perform a validation protocol, in one sense I am not *revalidating* the old cleaning process. What is really happening is that I am validating *for the first time a new* cleaning process (even though the new process may have many elements of the old process, if I have made a significant change, it really is a new process). So, it is reasonable that we drop the term "revalidation" for this third case.

What about the other two situations? They are still activities worth doing (or at least activities worth considering). What could the concern be? Well, it's probably related to concern about revalidation (or for that matter validation) being a *one time* activity. It is clear that what we traditionally have called cleaning validation (IQ, OQ and 3 PQ runs, or at least traditionally 3 PQ runs) is not all there is to cleaning validation. Based on a shift in regulatory focus, there is more to validation than this. One new element is the various design and development efforts that go into selecting a cleaning process, including "prevalidation" studies. This is one reason why three validation runs, which has no statistical support for demonstration of consistency of a cleaning process, is still the most common requirement for cleaning validation (despite recent FDA changes, based on PAT, that three is no longer the "magic" number). The reason for this is that what demonstrates consistency is not just the three PQ runs, but also all the various prevalidation studies that were also done. (Note that perhaps this is a part of the problem, in that we traditionally viewed these studies as before the validation and not part of the validation effort.) Furthermore, consistency is further demonstrated by the post-PQ validation data that are collected, such as the data reviewed for the yearly "revalidation" review. The addition of the design/

development and routine monitoring aspects of validation are supported by the FDA draft process validation guidance.

Now, what is more relevant, to have a yearly review of data (a one time activity once a year) or a continuous review of data (such as trending charts and alerts)? By "continuous," what I mean is something more regular, like every batch, perhaps with a monthly summary. Certainly we don't want to wait until year-end when we could have discovered a potential problem much earlier by having a "continuous" data review. I actually believe that many companies do this continuous review, even though they still have a formal, "once a year" data summary (since I am not aware of a situation where a pharmaceutical manufacturer evaluated data at the end of a year and was surprised by a problem).

What about the situation with manual cleaning? Isn't it still required to have a yearly protocol run? Actually, this is not a regulatory requirement, but it is a response that many manufacturers choose to address regulatory concerns with the variability of manual cleaning processes. For example, the PIC/S document states that manual cleaning processes should be "reassessed" on a more frequent basis. What does "reassessed" mean, for it is not clear from the PIC/S document itself. As I've said, one way to deal with this is to have a yearly "revalidation" run (or as I prefer to call it, a "confirmatory" run). Is this the best way to assure consistency for a manual cleaning process? Some might suggest it is all we can do for manual cleaning, because we don't have the automatically recorded process monitoring that is possible with an automated cleaning process.

On the other hand, one thing that is often overlooked is the importance of a visual observation following cleaning as part of (or perhaps the main part of) routine monitoring for manual cleaning. Particularly in cases like a manual scrub where all surfaces are readily accessible for visual examination, this can be a powerful tool. I'm not suggesting here that visual examination alone should be used for measuring residues in a protocol (although that certainly is possible). What I am suggesting is that the major concern with manual operators is inconsistency in coverage of scrubbing (or brushing) the surfaces. If this occurs, then it usually can be picked up by visual examination after the cleaned surface is dry. It will be apparent as streaks of residue on the surface, with the streaks corresponding to patterns that would occur if overlapping, consistent cleaning actions were *not* used. Again, the purpose of visual examination in this monitoring function is not to say that the residues are below any calculated limit, but rather to be an indicator of *inconsistent cleaning practices*. As I generally repeat in my training seminars, the purpose of the validation protocol is to determine that the cleaning process, if done correctly, will produce residues below the acceptance limit. The purpose of routine monitoring (and this is true for either automated or manual cleaning processes) is to establish that the cleaning process is performed correctly (or to give an early warning that it may be performed incorrectly).

So, where does this leave us with the "revalidation" issue? First, since the FDA is abandoning the term for process validation, it would be prudent to also consider abandoning the term (although I realize that this might be a slow process for the industry). Second, when we make a *significant* change to a cleaning process, just refer to that as "validation." As with any other validation, the old cleaning process might have valuable data that help provide assurance that the new cleaning process will perform consistently, so there is not necessarily a hard disconnect between the old and new processes. For example, the clean hold study that was done for the old process might still be applicable as a clean hold study for the new process (if the condition of the equipment at the end of each cleaning process and the storage conditions are essentially the same). Third, our focus on a "yearly" review should probably change to a "regular" review, which could be continuous (with perhaps a monthly summary). This is consistent with the FDA's emphasis on life cycle approaches to validation (Design, Formal Validation Studies, and Ongoing Controls) as well as to continuous improvement for manufacturing quality and efficiency.

The above chapter is based on a *Cleaning Memo* originally published in July 2008.

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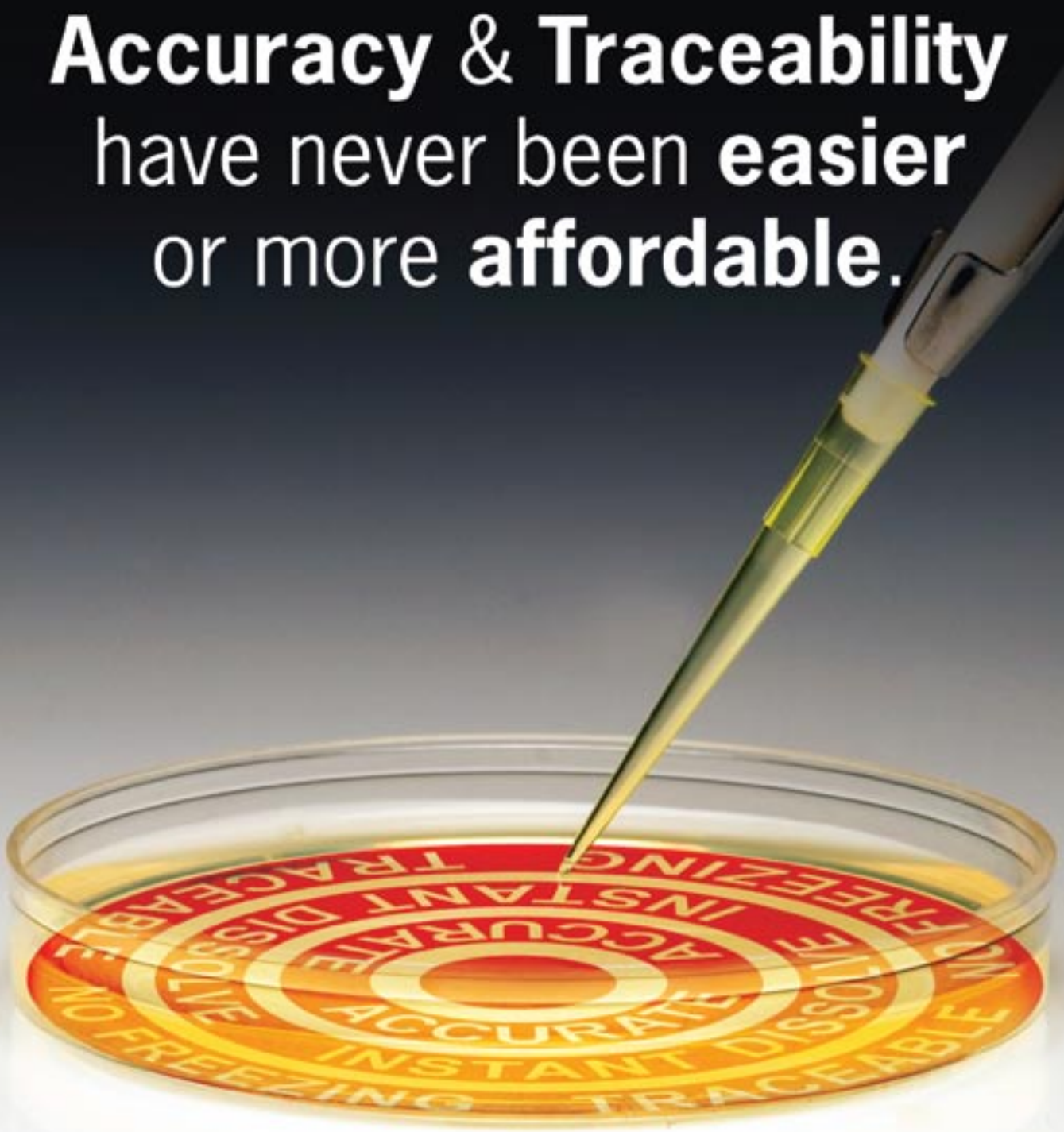

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Recent Sci-Tech Discussions: WFI Qualification, RQ of Equipment & Qualification of Tray Drier

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.

WFI Qualification

Under U.S. FDA guidelines I need to validate a purified water (PW) system for over a year to account for seasonality effects. Question: If I have validated my PW over the year, and I now decide to manufacture sterile product and install a distillation unit to make water for injection (WFI) to be used for my sterile product with this distillation unit getting its PW from my previously qualified PW system, do I need to qualify my WFI over a one year period or is it sufficient to perform a 7, 14 or 28 day qualification for the WFI generation and distribution loop (and how long should this qualification be)? After all I have qualified the PW over a year, and I know that it is stable despite seasons and this PW is the feed for the WFI.

Respondent 1: You need to qualify the WFI system for a period of 30 consecutive days.

Respondent 2: Who is right on this one? If you both cite the FDA guidelines, we can decide for ourselves.

Respondent 3: I had a similar case two years ago. If your validation data during one year shows consistency that your PW system is OK, there is no need to expend another year to demonstrate seasonal changes—that is the so called Phase III you have passed successfully and then you just keep normal monitoring. When you install your new WFI station you focus on it as your PW feed has been verified already, just do DQ, IQ, OQ, PQ in your still and WFI loop. A Phase I PQ should last for a minimum of 15 days with daily monitoring (including PW feed to the still). You cannot produce during this period, but you must analyze data, check and solve deviations and consolidate SOP's. Then starting Phase II PQ with another 15 days minimum. And if you demonstrate consistency during this, you can start the manufacture of your sterile product, no need for Phase III in this case. That is only if you make important changes in your PW station. With my very best regards.

Respondent 4: I think no need to take the qualification a year long. As input to the WFI plant has consistent quality as proved by your PW validation, hence seasonal variation shall not have any impact. Also review of routine trends of WFI will also support your not doing qualification for a year long. I will prefer to do it initially for 14 days or so to establish the SOP and then 28 days of monitoring with a SOP.

Respondent 5: Qualify the distillation plant and distribution loop for 30 continuous days, assuming no other piping modifications or additional use or sample points have been added.

Respondent 6: FDA's *Guide to Inspections of High Purity Water Systems*, "For water for injection systems, the samples should be taken daily from a minimum of one point of use, with all points of use tested weekly. The validation of the water system is completed when the firm has a full year's worth of data."

A PW system and a WFI system are really two separate systems and need to be validated separately especially for microbial attributes since the limits are vastly different.

Respondent 7: I assume that if you have a new WFI production system, you have also a new distribution loop. Considering that your previously validated PW system feeds your WFI, you have therefore validated your input. However, you do not know the capacity of your WFI system to consistently produce a water that meets the USP criteria nor your distribution loop to maintain the water quality over an extended period of time. I would therefore apply a conservative approach and validate the new WFI system over one year. Despite that you do not need anymore information regarding the seasonal variations, you will need this time to establish your alert and action levels for all critical parameters and also establish your PM program.

Respondent 8: If the incubation period is 18-72 hrs. Can I release the material in 40-50 hrs?

Respondent 7: The FDA guideline is correct. A PW system is not a WFI system. They are different. Thus, the issue here is that a new WFI system is being built. Again, FDA's *Guide to Inspections of High Purity Water Systems* states, "For water for injection systems, the samples should be taken daily from a minimum of one point of use, with all points of use tested weekly. The validation of the water system is completed when the firm has a full year's worth of data." The microbiology of a PW system is significantly different from that of a WFI system.

Doing anything other than a year's work is just delaying your warning letter and mass recall until you get caught, if the system does have seasonal issues you have never discovered. Save money now if you wish. Just budget for us to fix it later.

Respondent 3: Dear [Respondent 2], Did not fully understand. What did you mean with your posting? Anyway, I did not invent anything from my own and in the rush for answering [the Questioner]I forgot to point out the reference, it comes

precisely from FDA's *Guide to Inspections for High Purity Water Systems* which I think is still currently in force, In Part II "System Validation" the 3 phase validation scheme is stated. There is another WHO guide which states the same scheme but cannot remember now the exact reference. With my very best regards.

RQ of Equipment

This is with respect to requalification (RQ) of equipment. We have a RQ frequency of once in every 3 years for all the equipment. As part of this, we do OQ checks and then look into the history of the equipment for any changes, deviations/incidents, PMP etc and at the end conclude based on the above. Is it really required to do OQ checks during RQ? What I prefer to say is that the equipment is in a qualified state, I then review the history of changes made to the equipment, incidents etc and PMP and conclude that the equipment is in a qualified state. As the equipment is used daily, checking for one day during RQ for OQ checks does not make any sense, is what I mean. Is it mandatory to do so? Can anyone guide on this?

Respondent 1: I suppose it really depends on the criticality of that part of the process that the equipment is used for and if you base your requalification requirements based on a risk analysis. If the equipment you are talking about is a carton packing machine, you probably don't need to perform an OQ. A reviewing equipment history as you have outlined would be sufficient. If the equipment is, for instance, a sterilizing tunnel you may decide that the risk warrants an OQ.

Questioner: We work for OSD and the equipment is a sifter, multimill, blender, compression machine, coating machine, packaging machine and a cartonator. I don't feel any of these require OQ in RQ. Just for curiosity, I want to know why does a tunnel sterilizer require OQ in RQ as a batch processed daily is checked for its performance and operation?

Respondent 2: You described a frequency of 3 years which is quite a long interval for requalification. Anyway, it is better to perform not only an OQ but a PQ too in case of hot air sterilizer/depyrogenator/tunnel and autoclave. In case of the blender, you better perform OQ as the RPM may have changed (slowed) which results in improper mixing.

As far as your question about Tunnel (similar case in Autoclave), the cool point/s may change (increase) due to heater performance and any leaks that may have been produced in the duration. Similarly, the HEPA filter of the tunnel has to be checked annually for leakages.

These are very critical and I suggest you schedule the requalification of critical equipments to at least annual requalifications.

Respondent 3: If you do not think that you need OQ and RQ, what is your approach? Wait until things go wrong? I do not think that this will meet with most auditors approval.

Questioner: Dear [Respondent 3], Thanks for your reply. I do not mean that the things go wrong. What I do mean is that during RQ of equipment (which is set for 3 years) for an oral solid dosage facility, I will check the equipment history for its deviations/incidents, change controls raised and if there was any PMP carried out, breakdown, calibration verification, etc.

If you say RPM may change, we have a periodic calibration of RPM for all the blenders, coating pan, calibration of critical gauges, sensors for once in six months, non critical for once in a year. So the chance of things going wrong is absolutely ruled out as per my knowledge. And, moreover, during production of the batch, the operation of the equipment is performed and if any breakdown will be reported through SAP and will be tracked during RQ of the equipment.

So do I need to do OQ in RQ? Is it still mandatory? Only question, one auditor says "yes" and all have to follow, that is not wise, I think. I feel there should be some better idea for performing this rather than filling documents and consuming energy.

During RQ, I conclude, based on the PMP, calibration verification, change controls, incidents due to the equipment, breakdown, etc., which will say whether the equipment is in a qualified state. If not, I will call for complete qualification based on the summary.

Does this not suffice for a RQ which says the equipment is in a qualified state? I am not convinced with the answer of "do it." Can anyone give a sound reason why it is mandatory to do an OQ in RQ if I follow the above procedure?

Respondent 4: Hello [Questioner], You have good points to not perform actual "OQ" tests for the purposes of requalification. However, a fundamental mistake is concluding with a presumption, such as your view of the impossibility of "things going wrong." This is tantamount to…an approach to violation of GMPs, meaning a reactive rather than a proactive approach to avoiding failures. As [Respondent 4] has stated, "...waiting for things to go wrong" and they eventually will, GMP auditors/regulators will unlikely to accept your approach.

Through your deviation/change control events would any major change impacting a primary process step, which probably impacts the setup parameters and possibility the process parameters of the relevant equipment, not warrant engineering tests post change/modification? If so, would this not be a precursor to a requalification (OQ) of said equipment?

If GEP is adhered to then some physical testing would be required, which infers the need for OQ tests for requalification.

Any type of sterilizer is a critical process step. Regulatory expectation is for you to demonstrate a clear and accurate approach to maintaining this process step in a state of control, i.e., qualified/validated, in order to operate the equipment under normal production conditions. Further, the thermal loads/conditions to tunnel sensors (physical damage) and HEPA filters (sealing, holing, leakage, etc.) can invalidate your "validated" cool and hot control zones (gas, temp., pressure, airflow, etc.) under normal use. By preempting and proactively anticipating the diminishing ➤

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1 United States Pharmacopeia Convention, Inc. 2009. The United States Pharmacopeia 32/The National Formulary 27. 2009. The United States Pharmacopeial Convention, Rockville, MD.
2 European Pharmacopeia, 6th Edition. European Directorate for the Quality of Medicine, Council of Europe, 226 Avenue de Colmar BP907, F-67029 Strasburg Cedex 1, France.
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conditions through the rate of use against "validated" process conditions through the assessment for the risk of failure to equipment, process, product and the cost of your investigation will probably far outweigh the implications of product and regulatory issues in the long-term.

Simply, if you disagree with a GMP auditor/regulator, you need to present a very good argument supported by defendable evidence citing the relevant regulations have been met.

Questioner: Dear [Respondent 4], I completely agree with your comments. Any changes made to the equipment are documented and a risk assessment and RQ is performed accordingly (which includes OQ, PQ depending on the change made). But the case here is routine. RQ performed once in 3 years as part of our VMP. During this RQ is it mandatory that OQ be performed again or just a review of the history of equipment for its changes, incidents, PMP, calibration etc? Does it not suffice to say that the equipment is in a "qualified" state?

Respondent 4: Hello [Questioner], Taking requalification in isolation for process equipment, then making the assumption that your 3-year interval is a blank interval for all equipment, in my experience would not be acceptable… for an auditor or regulator. If this risk is acceptable to you then the consequences are acceptable also.

Have you performed a process step criticality assessment for your products/equipment? This will class the associated equipment to be critical too and be defined in the VMP too. Subsequently, the revalidation program should take this assessment into account and establish appropriate shorter and longer intervals. Do you revalidate a materials storage refrigerator every three years too? In a past life, I have established a revalidation intervals from six months to five years for process equipment, without consequences when audited or inspected.

In not assessing the risks involved with product, process, efficiency, compliance, etc. (i.e., current industry practice), it may be construed as not applying current good practice as expected by auditors/regulators. Simply, are you prepared to take the risks with your current regime?

Respondent 5: I'm sorry to disappoint the validation folks (I have a kinship with fellow consultants but don't like to overwhelm clients with extras that aren't necessary), but once you have a validated process RQ doesn't need OQ as long as the equipment train has remained intact. The purpose of validation is to show the equipment can perform its functions repeatedly over time. Reassessing it once a year, in conjunction with the production history from that year, is sufficient to show it has remained validated.

I was on a recent audit and reviewed two validations for two different autoclaves. The latest validation (2008) on the new piece of equipment was contained in three volumes and it took me a half hour just to decipher where the load configurations were. The earlier validation (2004) on an older piece of equipment was contained in a one inch notebook and showed me on the second page the load configurations, a summary of the thermocouple and BI placements and a summary of the runs that were conducted. Which validation was better? They were equivalent except one was much, much easier to understand.

I believe in the KISS principle (Keep it simple silly) and feel too much information, data (e.g., why do temperatures have to be recorded every single second—what benefit is it other than to fill a binder?) and retesting is not only gratuitous but also undermines the original validation efforts that were conducted.

Forgive me for the rant, but we live in an industry that is already highly regulated. Why make it even more difficult and expensive, to do the right thing?

Respondent 4: Hello [Respondent 5], Oh, I am with you on the KISS principle, though I know it as "keep it simple [silly]." I too had similar findings on audits performed in the past. Unfortunately, the misnomer "great mounds of paper" still rings true today particularly with supplier performed validation/revalidation activities for clients with less GMP validation knowledge. You could call it a "smoke screen." The end result is mounds of documents (i.e., generally lacking traceability) bulking up the validation documentation (i.e., loses value) that provides a "comfort level" to a client that the equipment has been appropriately validated. Why? In practice, a client probably depends (or assumes!) on the supplier being the equipment "expert" to have the said equipment validated.

I dare say to do the right thing takes more than just knowledge but the patience and courage to communicate to senior colleagues to better understand and appreciate the business and compliance risk involved.

Respondent 6: One of the problems that must be considered is that some equip-

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ment items get classified into an OQ that may need to be confirmed with a RQ. Equipment alarms are a good example. Too long in phase alarms in sterilizers and over-temp alarms in incubators can be included in OQ and be skipped with subsequent RQ. I think it is wise to review the original OQ list and confirm that any important system checks have been either moved into separate calibration, maintenance or monitoring SOPs or get repeated in the RQ.

Respondent 7: Hi, [Respondent 5], I fully agree with you. I have seen quite a few validation documents where people invest time and money to create a bulky document and the critical information is not at all part of that document (such as not capturing the speed, not checking the adequacy of filter on a direct contact compressed air etc.). Instead, making a few page documents to include the critical parameters is great value addition for whatever is done.

Also I think there is no point in wasting time to decide whether to do this in OQ/PQ… Q?, as long as it is done and documented (either in IQ/OQ/PQ) before the equipment is released to use, it should be OK.

Qualification of Tray Drier

I have a doubt regarding the qualification activity. The qualification of a tray drier is carried out and during the PQ I carried out with starch at different temperatures and checking LOD. Now as drying is continued at different temperatures, there is reduction in LOD and it is satisfactory in that way. But when I compare the LOD values in the same location of the tray and from different locations, the range observed to be 3.0% at each set temperature.

Is there any limit that defines the limit for such cases? Can anyone of you guide how you do the activity and what is to be done apart from this?

Respondent 1: Dear [Questioner], Differences in LOD is to expected with different heat transfer and drying rates at different locations and cake depth.

Drying is going from top to bottom at highest speed at edges of the tray and shelf. If you don't dry to equilibrium as you probably don't, there are differences in water content.

The water content is therefore lowest at the top of the cake at the corners. The water content in the final product has to be identical to what you have to introduce a validated homogenizing/mixing step before finalization of the production demonstrating homogeneity of the final product.

The observed LOD range observed after freeze-drying shall be demonstrated to be without quality impact for the relevant time period.

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.

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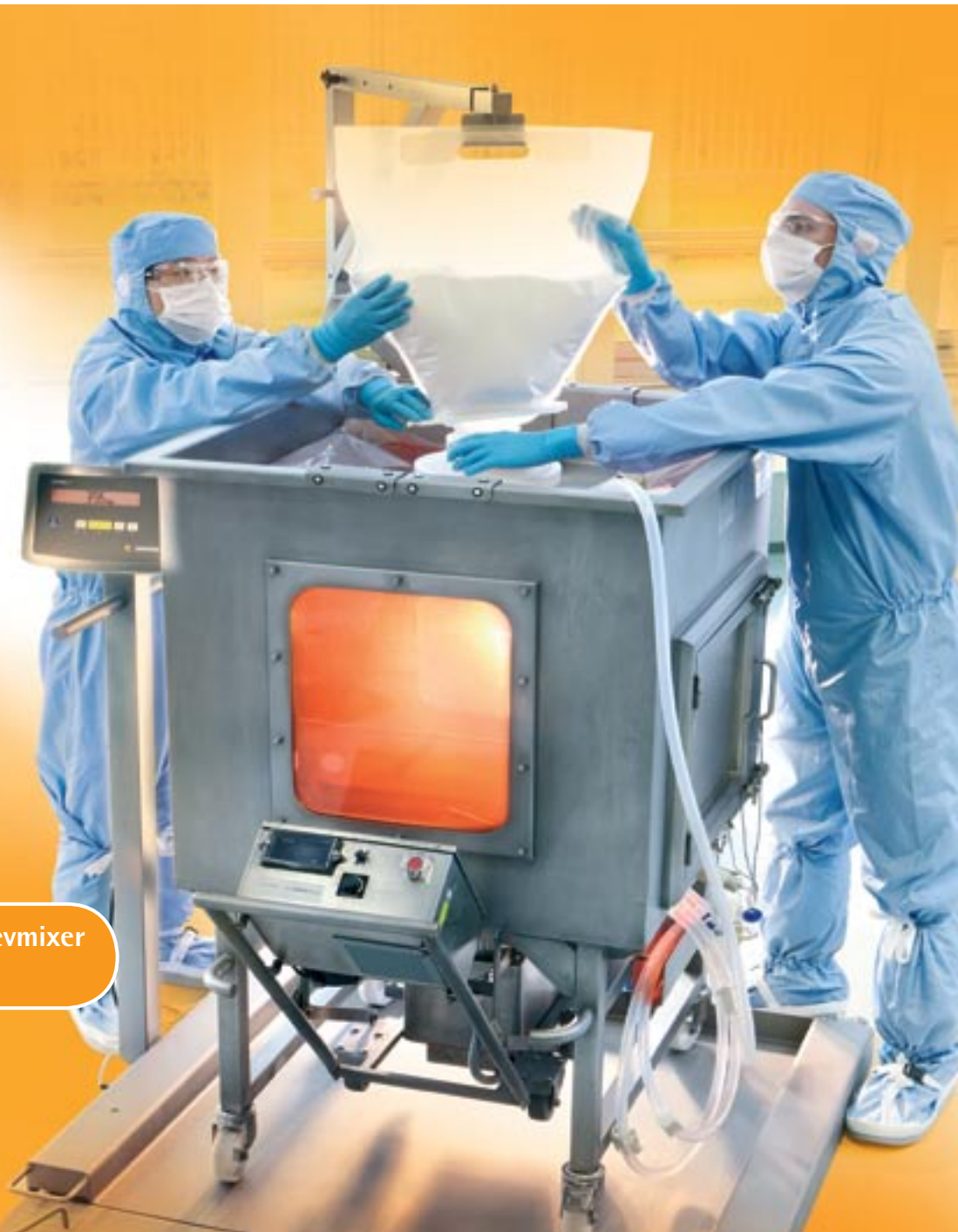

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Pharma's Reaction to Health Care Bill Mixed, continued from cover

PhRMA stated it had some concerns with the health care bill, pointing directly at "the overly broad powers of a non-elected Independent Payment Advisory Board," which would set prices of prescription drugs through the U.S. Medicare program. According to other reports found easily on the Internet, other groups including the American Hospital Association, the Association of American Medical Colleges and the American College of Surgeons also apposed this stipulation.

Ultimately, PhRMA sees opportunity through future legislation to aid the industry in bringing new medicines to the marketplace. "Most importantly, we must also take steps in the years ahead to support critically needed innovation, ensuring future medical advancements and breakthroughs. Americans deserve no less. New, cutting-edge medicines have dramatically increased life expectancy rates all across our nation and allowed patients to live longer, healthier and more productive lives. We remain totally committed to seeing this progress continue, benefiting Americans for generations to come."

GPhA Cool on Reform

In the very first sentence of its reaction to the House's historic vote, GPhA President and CEO Kathleen Jaeger stated, "Today's passage of health-care reform in the House provides both good and bad news for consumers."

On the good side, according to the trade group, access to generic medicines will expand for U.S. seniors, "thanks to a fix to the so-called doughnut hole"— a gap in Medicare Part D coverage that requires seniors to pay for all drugs costs out of pocket between $2700 and $6100 annually.

The group also supports the elimination of the patent settlement provision from the bill, which "would have had the unintended consequence of delaying generic access."

The remainder of the statement focused on the negative.

"The bad news is that the bill provides a biogeneric pathway in name only, giving false hope to patients who desperately need access to life-saving biogeneric medicines. Simply put, the bill fails to infuse competition and choice into the health-care system due to the excessive and unprecedented market exclusivity protections for the brand industry."

The legislation arrived on President Obama's desk on March 23

GPhA wants to see the closing of the "brand evergreen loophole" and the end to "brand biologic monopolies."

Ultimately, GPhA feels the legislation hinders generic access rather than helps. "In sum, while FDA has been given the flexibility to create a workable biogenerics approval pathway, the fact is that the brand market exclusivity protections in this bill — which supplement the robust, rich patent protection of these brand biologics — will keep affordable biogeneric medicines from patients for decades to come."

BIO Supports Reform

A statement released by BIO President and CEO Jim Greenwood touted the legislation's provisions that will boost efforts to bring new biotechnology-derived therapies to the market, and in contrast to GPhA's statement, bring biosimilars to the market.

"The health care reform bill passed by the House of Representatives last night includes key provisions that provide real solutions for our nation's health care challenges and real hope for patients living with debilitating diseases such as cancer, Multiple Sclerosis, Parkinson's, HIV/AIDS and many rare diseases. These provisions will lead to new and improved treatments, cures, and cost-savings for patients, while driving job growth in our industry and maintaining our nation's global leadership in biotechnology innovation."

On Biosimilars, BIO noted an "historic provision which creates a pathway to enable the U.S. Food and Drug Administration to approve biosimilars." The group explained that this provision will expand access "to safe and effective cutting-edge medical therapies at lower costs."

BIO also praised a component of the legislation called the Therapeutic Discovery ➤

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Project Tax Credit, which "will provide some financial relief to research-intensive, small biotechnology companies that continue to suffer from tight credit markets." Activities eligible for the tax write-off include "hiring scientists and conducting clinical studies." BIO projects that "this provision promises to save and create thousands of jobs across our nation."

GPhA Statement on House Passage of Health Reform Bill March 21, 2010

The Generic Pharmaceutical Association today released the following statement by GPhA President and CEO Kathleen Jaeger on House passage of the Health Care and Education Affordability Reconciliation Act of 2010:

"Today's passage of health-care reform in the House provides both good and bad news for consumers. The good news is that more Americans will have health-care coverage and more seniors will have access to generic medicines, thanks to a fix to the so-called doughnut hole. GPhA is pleased that the House has taken these steps to close the Medicare drug coverage gap and has eliminated the patent settlement provision that would have had the unintended consequence of delaying generic access.

"The bad news is that the bill provides a biogeneric pathway in name only, giving false hope to patients who desperately need access to life-saving biogeneric medicines. Simply put, the bill fails to infuse competition and choice into the health-care system due to the excessive and unprecedented market exclusivity protections for the brand industry. Until the brand evergreen loophole is closed and the indefinite brand biologic monopolies are addressed, our health-care system will not see true savings from biogenerics for decades. This is a very unfortunate missed opportunity that poses significant exposure to the sustainability of private and public pharmaceutical coverage programs. With so many Americans denied access, GPhA is committed to opening up this market to achieve timely consumer access to affordable biogeneric medicines. In sum, while FDA has been given the flexibility to create a workable biogenerics approval pathway, the fact is that the brand market exclusivity protections in this bill – which supplement the robust, rich patent protection of these brand biologics -- will keep affordable biogeneric medicines from patients for decades to come."

GPhA represents the manufacturers and distributors of finished generic pharmaceuticals, manufacturers and distributors of bulk active chemicals and suppliers of other goods and services to the generic drug industry. Generics represent 74 percent of the total prescriptions dispensed in the United States but only 22 percent of all dollars spent on prescription drugs. For more information about the industry, visit www.gphaonline.org.

PhRMA Statement on Health Care Reform March 21, 2010

The Pharmaceutical Research and Manufacturers of America (PhRMA) issued the following statement today on passage of comprehensive health care reform and accompanying reconciliation legislation in the U.S. House of Representatives:

"We continue to believe that comprehensive health care reform will benefit patients and the future of America. That's why we have been involved in this important public policy debate for more than a year and why we support action by the House to approve the Senate-passed bill along with the amendments found in the reconciliation legislation.

"The existing barriers to quality health care simply are not acceptable. Today's important and historic vote in the House will help to expand health care coverage and services to tens of millions of Americans who are uninsured and often forced to forego needed medical treatments.

"Our commitment to help pay for health care reform will require all of our companies to make some difficult choices moving forward – on top of already losing more than 150,000 jobs since 2007 because of the recession and other economic factors.

"But throughout this long process, we have been guided by a belief that all Americans should have access to high-quality, affordable health care coverage and services. This legislation, while not perfect, is a step in that direction.

"Even as we support health care reform legislation, we continue to have concerns about a number of issues including the overly broad powers of a non-elected Independent Payment Advisory Board (IPAB), which could enact sweeping Medicare changes without action by Congress and would not be subject to judicial or administrative review. We look forward to working with Congress to address these concerns and to identify ways to contain medical costs without creating new barriers to quality health care.

"Most importantly, we must also take steps in the years ahead to support critically needed innovation, ensuring future medical advancements and breakthroughs. Americans deserve no less. New, cutting-edge medicines have dramatically increased life expectancy rates all across our nation and allowed patients to live longer, healthier and more productive lives. We remain totally committed to seeing this progress continue, benefiting Americans for generations to come."

BIO Statement on Health Care Reform March 21, 2010

Biotechnology Industry Organization (BIO) President and CEO Jim Greenwood released the following statement after passage of "The Patient Protection and Affordable Care Act of 2009" by the U.S. House of Representatives:

"The health care reform bill passed by the House of Representatives last night includes key provisions that provide real solutions for our nation's health care challenges and real hope for patients living with debilitating diseases such as cancer, Multiple Sclerosis, Parkinson's, HIV/AIDS and many rare diseases. These provisions will lead to new and improved treatments, cures, and cost-savings for patients, while driving job growth in our industry and maintaining our nation's global leadership in biotechnology innovation.

"The bill includes a historic provision which creates a pathway to enable the U.S. Food and Drug Administration to approve biosimilars. Thanks to the leadership of Representatives Anna Eshoo (D-CA), Jay Inslee (D-WA) and Joe Barton (R-TX) in the House, and the late Senator Ted Kennedy and others in the Senate, patients living with debilitating diseases will have expanded access to safe and effective cutting-edge medical therapies at lower costs. Additionally, according to the Congressional Budget Office, this provision will save patients tens of billions of dollars over the next decade. Moreover, this provision includes the incentives necessary to attract the massive investment required to speed the discovery and development of the next generation of breakthrough therapies and potential cures for the world's most debilitating diseases. This language establishes equity with the Hatch-Waxman regime, which spurred the availability of the generics market for traditional pharmaceuticals, while bringing the same benefits of increased access, lower costs and expanded competition.

"The bill also includes a critical provision that will provide some financial relief to research-intensive, small biotechnology companies that continue to suffer from tight credit markets. The Therapeutic Discovery Project Tax Credit included in the bill will help offset a portion of the resources spent on therapeutic development activities, including hiring scientists and conducting clinical studies. The provision will help these companies continue their groundbreaking research that likely will lead to new therapies to treat patients living with chronic or acute diseases and help reduce long-term health care costs. This provision promises to save and create thousands of jobs across our nation.

"We look forward to continuing to work with the Congress to ensure passage of the reconciliation bill and effective implementation."

2010 PDA Upcoming

For an updated PDA calendar of events please visit *www.pda.org/calendar*

APRIL

6-8 **2010 St. Louis Course Series**
St. Louis, Missouri
www.pdatraining.org/stlouis2010

7-9 **Cleaning Validation**
Bethesda, Maryland
www.pdatraining.org/cleaningval

12-15 **2010 PDA Pharmaceutical Cold Chain Management Conference and Course**
Bethesda, Maryland
www.pda.org/coldchain2010

13-14 **PDA Workshop on Filtration**
Berlin, Germany
www.pda.org/europe

13-14 **2010 PDA Conference on Endotoxins**
Barcelona, Spain
www.pda.org/europe

15 **Interest Group Meeting: Pre-filled Syringes**
Berlin, Germany
www.pda.org/europe

20-21 **PDA Workshop on Biofilms**
Frankfurt, Germany
www.pda.org/biofilms

22 **Interest Group Meeting: Visual Inspection**
Frankfurt, Germany
www.pda.org/europe

22 **PDA Europe Workshop: Preparation of Virus Spikes used for Viral Clearance**
Frankfurt, Germany
www.pda.org/europe

26-28 **PDA/FDA Supply Chain Workshop**
Bethesda, Maryland
www.pda.org/supplychain2010

27-28 **Workshop on Container Closure Systems + Annex 1**
Berlin, Germany
www.pda.org/europe

28-30 **Development of Pre-filled Syringes**
Bethesda, Maryland
www.pdatraining.org/prefilled

MAY

4 **Interest Group Meeting: Freeze Drying**
Cologne, Germany
www.pda.org/freezedrying

5-6 **Workshop on Flexible Immediate Containers**
Berlin, Germany
www.pda.org/europe

5-6 **Integration of Risk Management into Quality Systems – Extended**
Bethesda, Maryland
www.pdatraining.org/integration

5-7 **Environmental Mycology Identification Workshop**
Bethesda, Maryland
www.pdatraining.org/mycology

7 **Achieving CGMP Compliance During Development of a Biotechnology Product**
Bethesda, Maryland
www.pdatraining.org/achievingcgmp

11-12 **An Introduction to Visual Inspection**
Bethesda, Maryland
www.pdatraining.org/AIVI

13-14 **Choosing the "Right" Microbial Identification Program for Your Biopharmaceutical/Pharmaceutical Quality Control Laboratory**
Bethesda, Maryland
www.pdatraining.org/microID

17-20 **PDA Vaccine Conference and Courses**
Bethesda, Maryland
www.pda.org/vaccines2010

17-21 **Aseptic Processing Training Program – Session 3**
SOLD OUT
(Week 2: June 14-18)
Bethesda, Maryland
www.pdatraining.org/aseptic

20 **Workshop on Preparation of Virus Stocks used in Virus Reduction Studies**
Frankfurt/Langen, Germany
www.pda.org/europe

24-26 **2010 Boston Course Series**
Boston, Massachusetts
www.pdatraining.org/boston

Events

Save These Dates

JUNE

2-4 **Q-IWG Training Workshop for ICH Q8, Q9, Q10**
Tallinn, Estonia
www.pda.org/europe

2-4 **Developing a Moist Heat Sterilization Program within FDA Requirements**
Bethesda, Maryland
www.pdatraining.org/DMHS

3-4 **Elements of Risk Management**
Bethesda, Maryland
www.pdatraining.org/elements

8-9 **Conference on Cleanrooms/ RABS/Isolators**
Basel, Switzerland
www.pda.org/cleanrooms

10-11 **Aseptic Technologies Conference**
Basel, Switzerland
www.pda.org/europe

15 **PDA Workshop on Advanced Medicinal Therapies**
Berlin, Germany
www.pda.org/ATMP2010

16 **PDA Vaccines Workshop: New Technologies for the 21st Century**
Berlin, Germany
www.pda.org/europevaccines

17-18 **PDA 3rd Monoclonal Antibodies Workshop**
Berlin, Germany
www.pda.org/MAb2010

21-22 **Pre-filled Syringes Interest Group Workshop**
Carlsbad, California
www.pda.org/calendar

22-23 **Contract Manufacturing Conference**
Amsterdam, Netherlands
www.pda.org/europe

23-25 **Fermentation/Cell Culture Technologies Training Workshop**
Bethesda, Maryland
www.pdatraining.org/fermentation

JULY

20-23 **Downstream Processing: Separations, Purifications and Virus Removal**
Bethesda, Maryland
www.pdatraining.org/downstream

26-30 **Basic Microbiology for Aseptic Processes**
Bethesda, Maryland
www.pdatraining.org/basicmicro

Web Seminars April–June, 2010

April

- 8 Knowledge Management: Application of Project Management and Program Management Best Practices to Lean Manufacturing and Lean Laboratory Projects
- 8 Software Implementation in One Third of the Time and Cost
- 13 Process Validation Excellence – It's as Simple as 1, 2, 3
- 15 Bioreactor Process Monitoring for Early Detection of Mollicutes Utilizing a Novel Sample Preparation Technology Coupled with Real-Time Transcription-Mediated Amplification
- 21 Adopting ICH Q10 to Achieve Competitive Compliance
- 22 Virus Clearance
- 27 Innovative Biotech Facilities – Modern Modular Manufacturing
- 29 High Efficiency Single Use Mixing Systems for Biopharmaceutical Applications

May

- 6 Coupling USP Methods and Automated Characterization Techniques to Facilitate a Quality by Design Approach
- 11 Fermentation Cell Culture Technologies
- 13 Automated Validation Lifecycle Management – A Working Model
- 18 Integration of an ISO 13485: 2003 Quality System into an Existing QSR Facility
- 27 In-line E-Beam Tunnels in the Medical Device and Pharmaceutical Industries

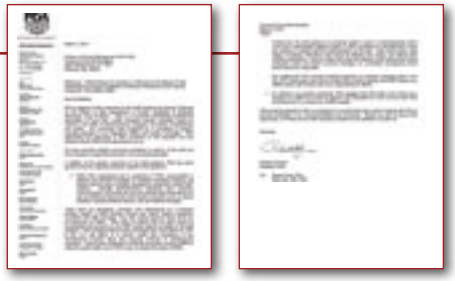
June

- 8 Down Stream Processing
- 10 Supplier Qualification: Auditing/Products and Services
- 10 Current Perspectives in Biofilms Growth
- 17 The Employment of PAT-based Manufacturing Science to Solve Capacity Constraints and to Increase Production Efficiency
- 22 Analytical Method Transfer Strategies for a Contract Manufacturing Organization
- 24 Filtration of Cell Culture Media with Enhanced Mycoplasma Retention and Filter Capacity

For a full list of upcoming PDA Web Seminars please visit: *www.pda.org/webseminars*

PDA Not Sure of FDA's Role in Drug Shortages, Per Comments on Absenteeism Guide

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



March 4, 2010

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

Reference: Draft Guidance for Industry on Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products; Docket No. FDA-2009-D-0568

Dear Sir/Madam,

PDA is pleased to offer comments on the draft Guidance for Industry "Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug 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, including members of our Regulatory Affairs and Quality Committee. PDA appreciates the opportunity to offer comments on this proposed rule and wishes to thank FDA for the opportunity to do so.

We have provided detailed comments identified by section of the draft and have included a supporting rationale in the accompanying table.

In addition to the specific comments on the draft guidance, PDA has some general concerns regarding particular aspects of the guidance.

- While PDA understands and is supportive of FDA's responsibility to address and alleviate shortages of medically necessary products, we believe that this issue is already managed by companies outside GMP systems. Typically pharmaceutical companies have "business continuity plans" which take into account potential high absenteeism as well as additional factors that could impact production such as natural disasters, equipment/facility failures, and raw material shortages.

These plans are developed, reviewed, and implemented as a business process outside of GMP systems though they clearly support operations consistent with GMP principles. They also include plans for areas which are not governed by GMPs. PDA does not believe that the plan should be incorporated and governed by the GMP quality system as stated in the draft guidance. PDA considers that the intent and legal basis of the GMPs (21 CFR § 210, 211 and 600's) is to ensure control and consistency of the manufactured products rather than assuring continuity of manufacturing operations. Assuring the availability of medically necessary products (MNP) is critical for public health, but in PDA's view, is outside the scope of GMPs.

Furthermore, the draft guidance as presently written is open to misinterpretation which could have unanticipated negative impact on GMP compliance of manufacturers if they are required to actually test the implementation of the plan. Each event which could trigger a business interruption plan would be different and unique, and testing each would be impractical. Tying up a plant with small test batches could interrupt the normal production cycles and result in product shortages, an unintended consequence which would clearly be undesirable.

We suggest that FDA consider providing guidance on business continuity plans in the form of a white paper that would include other Centers dealing with MNP issues (e.g. CBER) where said Centers also carry responsibility for MNPs.

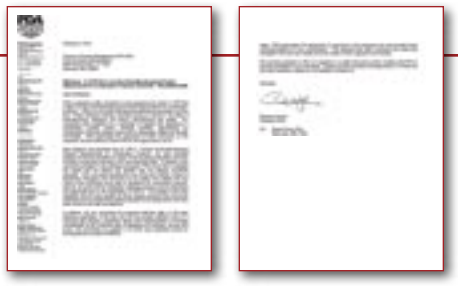
- As outlined in our specific comments, PDA suggests that FDA notify a firm if they are a producer of a MNP as it would be difficult if not impossible for a firm to know when they would become or no longer are, a MNP supplier.

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

Sincerely,

Richard Johnson
President, PDA

PDA Seeks Clarification of Existing Combination Products vis-a-vis Proposed GMPs



February 4, 2010

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

Reference: 21 CFR Part 4, Current Good Manufacturing Practice Requirements for Combination Products, Docket No. FDA-2008-D-0409

Dear Sir/Madam,

PDA is pleased to offer comments on the proposed rule under 21 CFR Part 4 titled "Current Good Manufacturing Practice Requirements for Combination 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 combination product issues, including members representing our Combination Products Interest Group and our Regulatory Affairs and Quality Committee. PDA appreciates the opportunity to offer comments on this proposed rule and wishes to thank FDA for the opportunity to do so.

With regard to the proposed rule 21 CFR 4, "Current Good Manufacturing Practice Requirements for Combination Products", we have provided detailed comments identified by section of the proposed regulation and have included a supporting rationale in the accompanying table. In addition to the comments provided in the attached document, PDA would like to highlight two issues that we believe are broader than the specific comments enclosed. First, we would promote the use of the term Hybrid in place of Streamline throughout the document as we believe this reflects the true nature of the combining of two sets of regulations for combination products. Second, we would ask for clarification regarding existing products developed and approved prior to the finalization of CFR 4. The impact of this new regulation will be much greater on those existing products that have been developed and controlled with existing regulations and agreements and have been proven to be safe and effective.

In addition, we are concerned the proposed effective date of 180 days following publication of the final rule will not provide sufficient time for a thorough gap analysis, systematic design and implementation of changes necessitated by the combined sets of regulations for biologics, devices and drugs, and accordingly we suggest a 12 month post publication period for the regulations to become effective.

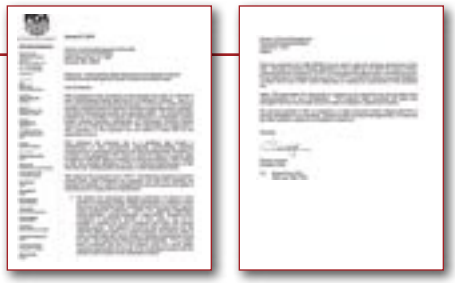
Again, PDA appreciates the opportunity to comment on this proposed rule and provides these recommendations for your consideration. PDA believes that these comments will clarify and strengthen the final rule to better serve the needs of both regulators and industry.

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 Johnson
President, PDA

Submission of Duplicate Safety Reports "Burdensome," PDA Says in Comments on Combo Safety Reporting



January 27, 2010
Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Reference: Postmarketing Safety Reporting for Combination Products; Federal Dockets Management System Docket FDA-2008-N-0424

Dear Sir/Madam,

PDA is pleased to offer comments on the proposed rule under 21 CFR Part 4 titled "Postmarketing Safety Reporting for Combination 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 quality, and regulatory affairs. Our comments were prepared by a committee of experts with experience in combination product issues, including members representing our Combination Products Interest Group and our Science Advisory Board. PDA appreciates the opportunity to offer comments on this proposed rule and wishes to thank FDA for the opportunity to do so.

PDA embraces this proposed rule as a significant step forward in establishment of FDA requirements regarding postmarketing reporting requirements for combination products and assuring appropriate information is provided to the designated FDA Center to allow the Agency to access data necessary to fulfill the Agency's mission of consumer protection. PDA is willing to offer any possible assistance to FDA in furthering implementation of this FDA final rule, including public workshops or other educational events.

With regard to the proposed rule 21 CFR 4, the following comments represent overall points noted throughout the proposed rule that PDA believes are important to address in order to strengthen this rule and improve the ability of manufacturers to comply with its requirements:

- We believe the requirement regarding submission of reports to both centers for sponsors holding multiple submissions in instances where they have not identified which constituent part led to the event, may be overly burdensome (reference section II.G. Separate Applications and/or Reporters - second paragraph - page 50749). Because of the complexity of combination devices, in many cases it may not be possible to identify the source constituent part within the shortest reporting period. We believe it would be less burdensome but still meet the Agency's needs if, in these situations, the primary mode of action should determine which Center's reporting requirements should be used. We suggest the following alternate language: "If it is unclear which constituent part led to the adverse event, you would satisfy reporting requirements for the part of the combination product with the primary mode of action of the combination product."

FDA also indicates Form 3486 (BPDR) may be used to meet the reporting requirements of the Rule. Although comments directly applicable to Form 3486 are not within the scope of FDA's comment period for proposed 21 CFR 4, we recommend the agency open a comment period for Forms referenced in proposed rules such as 21 CFR 4 to allow the industry to provide feedback on these forms due to their critical relationship to meeting the requirements of this proposed rule.

Again, PDA appreciates the opportunity to comment on this proposed rule and provides these recommendations for your consideration. PDA believes these comments will clarify and strengthen the final rule to better serve the needs of regulators, patients and industry.

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 Johnson
President, PDA

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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.

North America

FDA Seeks Suggestions for Improved Regulatory Transparency

The U.S. FDA is requesting comments on ways it can increase transparency between the Agency and the regulated industry. Specifically, FDA is looking for comments on how they can make improvements in training and education for regulated industry about the FDA regulatory process in general and/or about specific new requirements; the guidance development process; maintaining open channels of communication with industry routinely and during crises; providing useful and timely answers to industry questions about specific regulatory issues; and communicating with sponsors during review of applications.

Comments must be submitted by April 12.

U.S. FDA to Hold Public Meeting on Reauthorization of PDUFA

By September 2012 new legislation will be required to replace the expiring Prescription Drug User Fee Act (PDUFA) which enables the Agency to continue collecting user fees for the prescription drug program. Without new legislation, the U.S. FDA will no longer be able to collect user fees to fund the human drug review process.

Guidance on Cell Substrates Replaces 2006 Draft Guidance and 1993 Points to Consider Document

The U.S. FDA has finalized a draft guidance from September 2006 on the characterization and qualification of cell substrates and other biological materials used in the production of viral vaccines for infectious disease indications.

The finalized guidance provides recommendations to manufacturers of viral vaccines for the characterization and qualification of cell substrates, viral seeds and other biological materials used for the production of viral vaccines for human use. The *Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications* guidance replaces the information specific to viral vaccines for the prevention and treatment of infectious diseases that the Agency provided in the 1993 document entitled, *Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals*.

Guidance Recommends Information to be Included in Applications Pertaining to Parametric Release for Sterile Products

A newly released U.S. FDA guidance, *Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes*, provides recommendations on information to include in applications in support of parametric release for sterile products terminally sterilized by moist heat.

Agency Collection of Information on Shipments of Non-sterile Devices for Sterilization

The U.S. FDA is collecting information about the shipment of non-sterile medical devices for sterilization. Currently the Agency allows firms to manufacture and label these devices as sterile at one establishment and ship them in interstate commerce to another establishment for sterilization using an appropriate control mechanism. This control mechanism requires the preparation of agreements and maintenance of certain associated records.

The collection of Information will provide for the Agency an estimate of the burden on the industry to comply with these requirements.

Comments are due by April 19.

Key Regulatory Dates

Comments Due:

April 12
U.S. FDA requests comments on ways to increase transparency between the Agency and industry

April 19
U.S. FDA Collection of Information comments are due on the shipment of non-sterile medical devices for sterilization

May 10
Companies must submit proposed agendas to FDA for CDER's Regulatory Project Management Site Tours

Meetings:

April 12
A meeting will be held for the public to present its views on the reauthorization of PDUFA

Provide CDER Staff Exposure to Drug Development Processes – Invite Them to Your Plant

CDER's Regulatory Project Management Site Tours and Regulatory Interaction Program has been continued by the U.S. FDA. The goals of this program are to provide CDER staff first hand exposure to the industry's drug development processes and a venue for sharing information about project management procedures (but not drug-specific information) with industry representatives.

Interested pharmaceutical companies may submit proposed agendas to the FDA by May 10.

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The FDA recognizes swabbing as a preferred method for cleaning validation. Pharmaceutical companies rely on the quality and consistency of CleanTips® swabs from ITW Texwipe® for validating and verifying cleaning processes. Whether your test methodology is TOC, IMS, HPLC or UV-Vis, we have a validation swab that you can rely on to provide consistent results.

ITW Texwipe leads the way in critical environment contamination control products. From sealed-border sterile cleanroom wipers to laboratory notebooks to sterile IPA to kits for TOC testing, we have the right products for the pharmaceutical industry.

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Faster Profits in Slowing Economies

Don Schmincke

You cut, slashed, and hammered costs till your knuckles bled. Now what?

Is there another, perhaps faster, way to grow profits?

Research of successful companies find profits grow faster in challenging times with approaches contrary to typical slash and burn methods. Some of these approaches have ancient roots. It's not the first time organizations have encountered threats to their survival. And it won't be the last. But managing through this current episode may require to you to reconsider the typical approaches we so often use.

Analyzing 5,000 years of management history reveals a few insights that prove valuable in helping us thrive. These contrarian methods prove profitable by companies using them even today. Adding them to your arsenal may be the best decision you make. What can you do to learn from these leaders?

1 Stop Retrenching Strike Instead

Historically, economic downturns show winners don't retrench out of fear, but strike early. They accelerate their business by taking advantage of the fact that now their competition weaker than ever. But striking takes two things: Strategy and passion. Do you have a strategy? Are you sure? Studies find that most strategic plans end up being mere tactics. Avoid this mistake by:

- Calling a meeting with your staff.
- Laying out your strategic plan.
- Probing and challenging the assumptions. Does the plan show how you shall outmaneuver the competition? Does it show what position you seek in the competitive landscape? Or how you will exploit competitor weaknesses?

Getting strategy is only half the battle. What about passion? Our brains light up when we see something inspiring. Touchy-feeling mission statements are out. Sagas that inspire perseverance, unselfishness and sacrifice for the strategic win are in. It's not a new idea. It's been used for centuries. But we don't teach the crafting of stories anymore.

- Have you captured your strategy into a compelling saga?
- If not, condense your winning strategy into language that inspires passion for the strategic result.
- Then edit and re-edit. Remember, it's about crafting, not analysis.

Hire the brave, not the desperate. Samurai training found that cowardice stops leaders from challenging the status quo, holding others accountable and exposing weaknesses. Cowardice hinders decisive action by stopping the essential act necessary to accelerate profits and survive a recession—tell the truth.

2 Cowardice Eats Truth Lack Of Truth Eats Profits

Telling the truth can upset people, and desperate people don't dare risk it. Organizational cultures that promote bravery and the speed of execution that comes from it, love it. It drives accountability to new levels. The alternative of keeping the truth at unspeakable levels only produces collateral damage like:

- Accumulating dead-weight of marginally performing employees
- Avoiding the real issues thwarting meaningful change and profitability
- Sticking with doomed projects far too long

Strengthen your organization and enhance competitive advantage by enrolling and inspiring bravery.

3 Groupthink Is Good

We've been trained to feel that if everyone thought like us it would be a bad thing. In some cases that's true. But fast companies train their employees to think alike; they train them to think like a CEO.

Do your employees know how every decision affects the balance sheet? Field experience finds that employees placed in simulations where they have to run a company achieve new levels of understanding. With a balance sheet and a P&L statement in front of them, employees realize how every decision requires movements of cash. New perspectives forge as they have to decide how to go to market. What price? How much volume? Where do we advertise? Choices for growth and expansion become visceral and real.

Not surprisingly, these employees go back to their jobs with fresh insights on how their actions affect cash flow. They find money. They detect waste and inefficiencies. Opportunities for improvement surface which help companies needing to accelerate profitability.

4 Say "No" To Customers

Ancient battles were often won by knowing where to strike and where not to. There was an interesting story about Southwest Airlines. Co-founder of Southwest Airlines, Herb Kelleher received a scathing letter from a passenger

criticizing how they made jokes during the safety instructions required by the FAA. Fun is a key value at Southwest, and humor helps us pay attention versus falling asleep during these standard reviews. This particular passenger was not amused. Kelleher wrote back a one-sentence letter: "We're going to miss you."

How many times do you try to do too much for too many? Such mistakes stretch resources, distract strategic focus and decimate morale. Instead:

- Assess what the Return-on-Energy (ROE) is for your customer segments (how much profit customers bring for the total cost of selling and servicing them).
- Identify those clients whose ROE is minimum or, gasp, negative.
- Start writing "We're going to miss you" letters.

Eventually, and hopefully soon, we'll all emerge from the recession. Until then, don't hesitate to act now to accelerate your business. Remember, retrenching and waiting for it all to pass only gives your competition an opportunity to outrun you. Take the lead. Just because times are slow, doesn't mean you have to be.

About the Author

A dynamic speaker and author, Don Schmincke, began his career as a scientist and engineer. After graduating from MIT and Johns Hopkins University, he spent decades researching and applying anthropology and evolutionary genetics to management theories. He authored the bestseller *The Code Of The Executive and High Altitude Leadership* with co-author Chris Warner. Visit www.HighAltitudeLeadership.com for a free team assessment exercise.

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

Volunteer Spotlights

Claudio Puglisi, Technical Director – Qualified Person, Magis Farmaceutici S.p.A

PDA Join Date: 1999

Areas of PDA volunteerism: *Future of Validation* speaker (2000); *Adding Value to the pharmaceutical Industry Leveraging the Future* speaker (2002); PDA International Congress Program Committee member and session chairman (2003); PDA International Congress Program Committee Member and Session Chairman (2004); PDA International Congress Congress chairman and moderator of the Plenary Session (20005); PDA International Congress Program Committee member (2006); The Essence of *PDA/EMEA Joint Conference* moderator (2006); PDA International Conference Program Planning Committee member and session moderator (2007); *PDA International Conference* Program Planning Committee member and session moderator (2008)

Interesting fact about yourself: I have a masters degree in Pharmaceutical Chemistry and have spent 14 years in the production of parenteral drugs (traditional and B/F/S), solids and ointments. In 2006, I was awarded the PDA Chapter Volunteer Award. While not working, I enjoy listening to music, reading and traveling.

Why did you join PDA? In the beginning, I wanted to attend a PDA conference for my own needs. Over time, I understood the importance of being a part of the Association, to get involved in the volunteer activities of PDA.

Of your PDA volunteer experiences, which have you enjoyed the most? Being on the Program Planning Committees for PDA conferences, including the PDA European Congresses in Prague 2003, Rome 2004 and Basel 2005. I have also been involved in regional "Interchapter" meetings on IMPs in Paris 2008 & 2010 and Rome 2009.

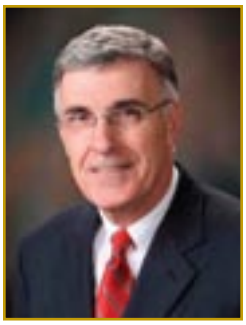
How has volunteering in PDA benefited you professionally? Volunteering at PDA means being in touch with many valuable people from the pharmaceutical world. This gives me the opportunity to be continuously updated on new regulations and technical trends.

Which PDA conference/training course is your favorite? The Annual Meeting, which covers so many hot topics and where I can participate with the different committees, task forces and interest groups. This way I have the opportunity for discussions with them face-to-face.

What would you say to somebody considering PDA membership? I would tell them to join PDA immediately. They will have the opportunity to be part of a great network. This way they can find answers to their questions and know any changes and news on pharmaceutical rules. I would also suggest they serve as committee member, speaker or/and interest group member, so they can be constantly in touch with very interesting people!

www.pda.org/spotlight

Nicholas R. DeBello, Director, Quality Management Systems, Wheaton Industries



PDA Join Date: August 29, 2001

Areas of PDA volunteerism: PDA Glass Task Force (Technical Report No. 43 and currently working on a revision to include ampoules, cartridges and syringes) Co-chair; PDA Glass Task Force

Interesting fact about yourself: I am a team player who is always searching for a better way to do something, and a by-product of this is that I am never satisfied until I have found a solution to a problem.

Why did you join PDA and start to volunteer? Being a supplier to pharmaceutical companies, I wanted to stay in touch with the industry, have a greater understanding of the technology and regulatory requirements, and learn more about future trends, best practices and expectations. As for volunteering, it was a way for me to be more involved in PDA and to share my knowledge, as well as meet and work with new and experienced individuals. Volunteering allowed me to be a part of a solution as opposed to just sitting on the sidelines.

Of your PDA volunteer experiences, which stand out the most? My first experience by far. It was my introduction into being an active participant on a specific project within PDA. Even though the project took longer than what I would have liked, it was a very rewarding experience being a part of a cross-functional team consisting of industry leaders and experts working together with a single focus in mind to develop a new guideline for the industry. In the end, we all received a great deal of satisfaction by seeing the results of our work come to fruition when PDA Technical Report No. 43 was finally completed and published.

How has volunteering through PDA benefited you professionally? My volunteer work has not only opened new doors for me, but I have also learned a great deal. In addition, it has also shown me that there is a continuous need for new guidelines in the industry to support our ever changing industry.

Which member benefit do you most look forward to? I have no one member benefit that I look forward to the most. The fact that I am a member of this organization enables me to take full advantage of all the opportunities that PDA has to offer.

Which PDA event/training course is your favorite? I find the Visual Inspection Forum and the Universe of Prefilled Syringes and Injection Devices Conferences to be very interesting and instructive. I have a great deal of interest in these two topics and the events are always very informative.

What would you say to somebody considering PDA membership? I would encourage the individual to join. The organization is a data bank of knowledge on subjects pertaining to industry technology, regulatory matters and practices. There is always a source that you can tap for information within PDA. Without a doubt the benefits that one obtains through their membership far outweighs the costs.

Please Welcome the Following Industry Leaders to the PDA Community

Vanessa Acosta, Genentech
Christer Alden, Mitthögskolan
Stale Ausen, Nexans
Nick Beaumont, Genentech
Aldo Bergamini, Sartorius-Stedim
Michael Bergren, JHP Pharmaceuticals
David Bonilla
Melissa Brewer, Sage Products
Matthew Brown, Lyosolutions
Qiang Cao, Becton, Dickinson and Company
Astrid Cardenas, Eli Lilly
Bruno Cocheteux, Sibaya BC Pharmed
Nilsa Colon, GlaxoSmithKline
Sean Cook, Sanofi Pasteur
Steven Cook, Pfizer
Jose Cortes
Donald Cunha, D&M Associates
Heribert Dahmen, Merck
Brian Damon, Amylin Pharmaceuticals
Cher Daun, Sage Products
Cindy Dawson, Ethox International
Jenifer Dean, Cell Trends
Mario Del Toro, Laboratorios Pisa
Maureen Dennehy, The Biovac Institute
Namalie Dewan, Biovitrum
Erik Dietrichson, Octapharma
Jacqueline Dombroski, AVI BioPharma
Nina Dorre, Algeta
John Dwiggins, Panther Expedited Services
Peter Eichert, Millipore
Hakan Ekwall, PB Teknik
Ernie Esparza, Edwards Lifesciences
Sabine Feig, Novartis Vaccines and Diagnostics
Stephanie Ferrante, Millipore
Emma Flynn, Emma C Flynn
Robert Foyt, JHP Pharmaceuticals
Shawn Gallagher, MG America
Peter Gannon, GE Healthcare
David Geer, Merck
Diane Guilbault, Consultpharm
Bob Haggerty, Hyaluron
Henning Hansen, Novo Nordisk
Catrin Hartleif, F. Hoffmann-La Roche
Eric Harvey, Aseptic Processing Consulting Services
Marie Hayes, Vistakon
Berit Helmfrid, Tetra Pak
Christopher Hill, Pall
Jean-Louis Horlait, GlaxoSmithKline
Ming Chia Huang, Vertex Pharmaceutical
Claudia Huerster, Boehringer-Ingelheim
Aidan Hughes, Pfizer
Kay Hunsberger, Merck
Nick Hutchinson, Parker Domnick Hunter
Modesto Ibanez, BBraun Medical
Vito Incandela, Sintetica
Cynthia Incorvati, Neoceram
Amber Jackson, Emergent BioSolutions
Michael James, Compliance & Validation Services
Karissa Jenkins, Sanofi Pasteur
Ernest Jenness, Millipore
Chris Jepsen, Genzyme
Jette Elkjaer Johansen, Novo Nordisk
Susanne Jorgensen, Biogen Idec
Ayelet Katzelnik
Mette Kjeldgaard, Aalborg Hospital Pharmacy
Mahesh Krishnan, Pfizer
Anil Kumar, Pall Life Sciences
Stephen Lang, Biogen Idec
Suzan Lanz, Savient Pharmaceuticals
Chun Pei Lau, Pharmaceutical Services
Bart Lievens, GlaxoSmithKline
Carolyn Lindsey, CareFusion
Brian Magensky, Ben Venue
Theodoros Makriyannis, Uni-Pharma
Angela Masino, Mentor
Christopher Mastroly, Cephalon
Walter Mateo, IBSA Institut Biochimique
Akira Matsuda, BioVigilant
Izumi Matsumoto, Biotest
Michael McDermott, Ingersoll Rand
Genevieve Motte, Nextpharma
Maha Nassar, Nassar Consulting
Nicole Nepomuceno, Sensitech
Lars Nielsen, Bavarian
Peter Nolan, Safety Syringes
Steven Novak, Genentech
Ama Veronica Onumah, Merck
Ed Orme, Wyeth
Stephen Orosz, ImClone Systems
Chakradhar Padala, Amgen
Venkata Palempalli, Aurobindo Pharma
Guangliang Pan, Eli Lilly
Ankur Patel, ImClone Systems
Matt Payne, Ritedose
Leland Perry, AVI BioPharma
Erica Polizzotto, GlaxoSmithKline
Claudia Protzner, W.L. Gore & Associates
Inger Rabb, Biovitrum
Joe Ranalletta, Baxa
Antonio Rico, Genentech
Dennis Roberts, Cell Therapeutics
Madeline Roche, Covidien
Michael Rose, Pfizer
Dax Rose, Astellas
Salil Saksena, Glenmark Generics
Anita Schnarrenberger, Pharmachemie
Victoria Scott, Discovery Laboratories
Dusty Snoeberg-Renwick,QRC
Joanna So, Genentech
Ritsu Sonohara, Astellas
Erin Sorrell, Talecris
Brian Stamper, MedImmune
Glenn Steinke, GlaxoSmithKline
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David Strong, Pfizer
Srikanth Sundaram, Eagle Pharmaceutical
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Kris Taylor, Allergan
Edward Thomas, Merck
Dana Thompson, Genentech

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Nathan Trembath, Hospira
Tomohiko Tsurumaru, Japan
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Stanislava Velikova, Hallmark
Ovid Villarreal, Amylin
Martin Vorborg, Biogen Idec
Christine Wadey, CSL Biotherapies
Joanna Ward, Seattle Genetics
Dixie Webster, Watson Pharmaceuticals
Andrew Weiskopf, Biogen Idec
Zai-Qing Wen, Amgen
Carol Whitinger, SoloHill Engineering
Barbara Wick, Becton, Dickinson and Company
Daren Wickland, Weiler Engineering
Kevin Wilkerson, GlaxoSmithKline
Jan Willems, Janssen Pharmaceutical
Reginald Williams, Salix Pharmaceuticals
Catherine Willis, Medical Developments
Stephen Winyard, Panther Expedited Services
Marco Wong, Proteon Therapeutics
John Wong, Genentech
Richard Wong, Baxter Healthcare
Amy Woodard, Ben Venue
Kelly Wyatt, Cook Myosite
Sharon Yarkoni, Omrix
Lenny Zacks, Validation
Anwar Zaman, Bayer Healthcare
Kevin Zhang, Abbott

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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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Change Your Paradigm: Attend the 2010 PDA/FDA Conference

Washington, D.C. • September 13-16 • www.pda.org/pdafda2010

Program Planning Committee Member Barbara B. Zinck, Zinck Consulting

Can September really be that far away? Not if you are anxiously awaiting the *2010 PDA/FDA Joint Regulatory Conference*. For many attendees and PDA members, the PDA/FDA annual meeting is *the* premier professional meeting of the year. It's difficult to call one PDA meeting the premier since PDA meetings are outstanding, but there are an extraordinary number of reasons to attend this meeting. Let's focus on a few of the many reasons why you and individuals from your company should attend this year's meeting.

Mark your calendars; the meeting is scheduled for September 13-16 in Washington D.C. This is one of the nicest times of the year in Washington D.C., since the temperature is just right (in the 70s) and not humid. You will want to arrive early to sightsee, since you will not want to leave the great meeting that starts early each day and ends late.

The conference theme is *The New Paradigm: Quality and Compliance in Merging and Emerging Cultures*. When you attend the meeting, ask the planning committee how they managed to fit so many buzz words in one phrase. Seriously, these are issues that pharmaceutical/biopharmaceutical/device professionals are dealing with on a daily basis. Companies are combining work forces and strategically managing change to be able to compete in a multinational marketplace while implementing and incorporating emerging global regulatory requirements.

This conference will discuss some of the challenges facing the medical products industry while navigating regulatory compliance, achieving worldwide quality improvement and enhancing quality system controls in an environment of merging and emerging cultures.

There are multiple sessions covering pertinent and interesting themes presented by FDA and industry experts. Some of the topics that will be presented include:

- Good distribution and supply chain practices for incoming materials
- Good distribution and supply chain practices for manufactured product
- Quality systems today as they relate to contract manufacturing.
- Managing product knowledge through product transfer activities
- The basic principles of the FDA Quality Systems, including:
  - CAPA
  - Managing regulatory inspections
  - Root causes for product recalls
  - Responsibilities of the quality unit

Since there are many interesting topics and more topics than one person can attend, companies should send multiple attendees to the conference. There are three major tracks focusing on foundations, quality today and merging and emerging. These tracks will benefit executive management, research & development, regulatory affairs, manufacturing, quality assurance/control, marketing, sales, supply chain and clinical supply material preparation professionals ranging from entry to experienced participants. Since the tracks run concurrently, your company should send multiple participants to the meeting to make sure that all of the important topics are attended.

The closing plenary continues the essential tradition of offering U.S. FDA updates by senior FDA officials covering regulatory updates, center direction initiatives and current 483 observations presentations from all centers including CBER, CDER, CDRH, CVM and ORA. If you want to stay current in your position and avoid regulatory problems, this is a must-attend session. Don't be caught not knowing the FDA's current thinking and expectations!

The meeting offers a conducive setting for networking with a chance to meet new colleagues and to catch up with old colleagues, including international colleagues. Networking is a valuable tool for working effectively in your current position and staying ahead in today's environment of merging and emerging cultures.

The *2010 PDA/FDA Joint Regulatory Conference* is relevant and timely with important information that should not be missed if you want to be successful. Please plan to join us in Washington D.C. on September 13 - 16 for a valuable learning experience.

Expand your educational experience with the post-conference workshop, *2010 PDA Extractables/Leachables Workshop: Container Closure Systems, Impact to Drug Product Quality* from September 15-16 and PDA Training and Research Institute courses on September 16.

For details on the conference, post-conference workshop and courses, please visit www.pda.org/pdafda2010.

Learn About the Importance of Prefilled Syringes

Las Vegas, Nev. • October 18-19 • www.pda.org/prefilled2010

Program Planning Committee Member Thomas Schoenknecht, PhD, Amgen

In October 2009, for a short time, the center of the prefilled syringe and injection device world was located in Venice, Italy where the sixth PDA conference on Prefilled Syringes and Injection Devices took place. Expert speakers representing various therapeutic classes in the pharmaceutical industry, leaders from the device and primary container world, as well as U.S. and European regulatory experts shared the latest industry and regulatory development trends. More than 400 participants from 24 countries representing 140 companies immersed themselves in the current and future parenteral drug delivery products and regulatory requirements. More than 50 exhibitors from the container, component, device and machine equipment industry presented their current products and provided detailed insights into future developments. Many of these future products appear close to be marketed and are targeted to address the needs and issues of this fast and constant evolving industry.

PDA's Universe of Prefilled Syringes and Injection Devices has become the central forum where industry representatives, component suppliers, equipment manufacturers and regulators share their knowledge and experiences

Pre-Conference Workshop on Glass to Discuss Quality Improvements

In addition to the main conference, a special preconference workshop was held one day prior to the main event. This was organized jointly by the International Commission on Glass, represented by **Fabio Nicoletto**, and PDA. The conference featured glass and its specific characteristics in pharmaceutical packaging applications. A panel discussion at the end of the workshop discussed the future role of glass for parenteral drug delivery and improvement areas addressing the needs of different therapeutic classes such as improved cosmetic quality, tighter geometric tolerances and consistent homogenous siliconization.

Two-day Training Course on Prefillable Drug Containers

A practical hands-on training with prefillable drug delivery containers was offered in a two-day course following the main conference. Participants could gain deep insights into basic technologies such as siliconization, filling and plunger stopper placement. The training also offered insight into the evaluation and interpretation of test results as well as good documentation practices to meet regulatory expectations.

Main Conference and Networking with Experts

The main conference consisted of 38 presentations given in three plenary and eight parallel sessions. The conference was opened by a series of four complementing presentations describing current and future market drug delivery products, their design space requirements and manufacturing challenges from the pharmaceutical industry end-user and delivery device vender perspective. The general theme of the opening plenary session was an increased cooperation between the suppliers of parenteral packaging products and the pharmaceutical industry to drive process optimizations to address the growing quality demands of new products and devices. A common theme ran through many talks on how quality requirements need to be jointly owned by supplier and pharmaceutical end user.

In parallel tracks, technology topics as well as marketing and business development aspects were discussed by expert speakers from the pharmaceutical industry. The latest rubber closures trends in sterilizing, as well as strategies addressing Japan quality requirements on rubber materials were discussed in one of the sessions. Another session was focused on track and trace technologies featuring the regulatory landscape in the U.S. and Europe, followed by two presentations describing case studies about the implementation of laser marking technologies to address pharmaceutical industries track and trace requirements.

A Spotlight on Safety and Quality

Other parallel sessions were focusing on the challenges of combining containers with add-on devices featuring the broad range of different device options for prefillable containers. The increasing demand for safety devices was documented by insights into the requirements for the implementation of needle stick safety devices with injectable drugs. The challenge of function versus design was also discussed during a presentation about injection devices providing insight of the potential pitfalls of the syringe/autoinjector combination. Those sessions featured new injector designs and lessons learned during high viscosity drug injection device application studies.

Manufacturing issues, extractable studies and best practices to meet current and future demands of a fill-finishing operation were discussed in a set of sessions. Particulate matter identification technologies as well as siliconization control studies (with the goal to reduce the drug contamination by silicone) were highlighted and engaging discussion ensued. A case study on the strategies and challenges during the development of a prefilled syringe drug offering for sensitive biopharmaceuticals was presented to a highly engaged audience.

Technology Trends

Inspection technologies and latest fill finish equipment options were discussed in sessions featuring trends and issues in pharmaceutical manufacturing. One talk featured high voltage leak detection during high speed visual inspection of prefillable containers. In-line E-Beam-sterilization tunnel applications were presented, as well as a case study about a high speed syringe filling line with disposable dosing system addressing the demand of high flexibility in syringe filling line operations.

Keeping Abreast of Regulatory Developments

The evolving regulatory landscape for prefillable drug delivery offerings and devices was described in detail by two expert speakers. **Daniel Mueller** from the Regierungspräsidium who is in charge of inspections in the south Western Region in Germany, provided an insider's view of the benefits of auditing pharmaceutical filling operations based on prefilled syringes. He clarified in his presentation the responsibility for the material used in syringe filling lies with the pharmaceutical manufacturer even when a ready to use material is utilized. **Kimberly Trautman** from the U.S. FDA expressed the Agency's approach of viewing devices and prefilled syringes as combination products and the need of pharmaceutical companies to apply relevant device regulations and guidelines on devices, as well as prefilled syringes.

In a panel discussion at the end of the conference, experts from the pharmaceutical industry and the supplier side discussed innovative drug delivery systems. Innovative products such as needle free drug delivery system were presented during the session. The experts closed the panel discussion with a universal statement about the need to understand and further develop therapeutic class specific drug delivery applications in partnership between pharma and suppliers to address the needs of the patients in the best way possible.

Looking Forward to This Year's Meeting

Looking back on this conference and having reviewed the participant and vender feedback, we can clearly say this conference highlighted once again the importance of prefilled syringes in the parenteral drug delivery world. The advantages in convenience and security for healthcare professionals and consumers, as well as reduced overfill and waste, are so convincing that the market for prefilled syringes continues to grow strong, as does the attraction of this conference. PDA's Universe of Prefilled Syringes and Injection Devices has become, over the last few years, the central forum where scientists, pharmaceutical industry representatives, component suppliers, equipment manufacturers and regulators can share their knowledge and experiences and network.

The next conference will be in the United States in Las Vegas from October 18-19 and we would like to ask you to mark your calendar for this important event. For more details about this conference and PDA TRI courses that will accompany it, please visit www.pda.org/prefilled2010.

For further information, please contact tschoenk@amgen.com or roessling@pda.org.

Role of Vaccines Discussed at Conference

2010 PDA Vaccine Conference • Bethesda, Maryland • May 17-20 • www.pda.org/vaccines2010

Program Planning Committee Member Kirsten L. Vadheim, PhD, BioCompliance Consulting

Vaccines have become a pillar of our public health strategy over the last century, as routine childhood immunization has effectively eliminated epidemics of once common diseases, such as diphtheria, polio and smallpox in the developed world. Recent scientific advances have expanded the potential of vaccines to include malaria, AIDS and cancer immunotherapies. Simultaneously, our expectations have risen to include the global reduction or even elimination of vaccine-preventable diseases.

It's an exciting time. In additional to the routine but exacting business of producing high-quality vaccines, industry and international regulatory agencies have worked intensively together to rapidly respond to emerging threats such as the H1N1 influenza pandemic. Long relegated to a niche market among pharmaceutical manufacturers, vaccines are now emerging as a significant growth industry.

Members of PDA's Vaccines Interest Group proposed a PDA meeting focusing on areas of particular interest to the vaccine industry and regulators as a reaction to these challenges and opportunities. The agenda for the *2010 PDA Vaccine Conference* includes experts from government, industry and non-government agencies to discuss topics that typically remain unaddressed in larger pharmaceutical meetings. The program is designed to target issues industry and regulators struggle with every day, providing the opportunity for in-depth discussions and identifying better paths forward.

The *2010 PDA Vaccine Conference, Today's Challenges, Tomorrow's Opportunities*, held on May 17-20, will open with two plenary sessions on the present and future role of vaccines. Speakers from the U.S. FDA, the National Vaccine Program Office and the Vaccine Development Global Program at PATH will highlight the present role of prophylactic vaccines in the public health, discuss vaccines designed to support the needs of the developing world and touch upon the challenges presented by overlapping regulatory agencies.

Sessions on Manufacturing Science and Quality (A1) and on Development and Regulatory Sciences (B1) will run concurrently. Session A1 will cover several topics related to current manufacturing processes, including the use of modular facilities, aseptic processing and validation of vaccine production processes. Talks in the Development and Regulatory Sciences session will review issues such as non-clinical testing requirements and product comparability. Challenges presented by vaccine testing strategies will also be discussed in a full plenary session devoted to analytical methods, with speakers discussing the application of Quality by Design to the testing of vaccines and the use of risk assessments, followed by a question and answer session.

Individual sessions reflecting the rapidly changing environment of the vaccine industry are included in all three days of the meeting. Presentations are scheduled on novel delivery and expression systems, new vaccine technologies and the regulatory challenges of developing new adjuvants.

2009 was a busy year for the vaccine industry with the H1N1 pandemic and the resulting challenges in the development, testing, production and timely delivery of an effective vaccine. These will be reviewed in a plenary session that will include a panel discussion of industry and FDA experts.

The meeting will close with a vaccine compliance update from the Center for Biologics Evaluation and Research and an opportunity for further questions and answers.

In all, these presentations offer an unparalleled opportunity to learn about the current status and future opportunities of the vaccine industry, as well as talk to regulators and colleagues about managing today's challenges.

The meeting will be held at the Bethesda North Marriott Hotel and Conference Center, a comfortable and well-equipped venue easily accessible within easy walking distance of the Metro Red Line.

It promises to be an excellent meeting, and we hope to see you there!

For more details about and to register for the conference and PDA Training and Research Institute courses that will complement the meeting, please visit www.pda.org/vaccines2010.

An Interview with TRI Instructor Barry Friedman

Stephanie Ko, PDA

[**Editor's Note:** The following is a question and answer between one of the TRI staff, **Stephanie Ko** and TRI instructor **Barry Friedman** about Barry's outstanding teaching history and his ability to keep students engaged in and out of the classroom.]

Stephanie: How were you initially contacted to be an instructor?

Barry: I have been an active member of PDA since the mid-90's and have participated in meetings and courses. I had observed that a one day microbiology of water course was not being provided that currently met the industry's needs.

Stephanie: When did you agree to teach?

Barry: I agreed to teach following "off and on" discussions over several years. It was not something that occurred within a period of several months.

Stephanie: When did you start teaching?

Barry: I have been teaching since I was a graduate student at Ohio State University. However, I only started teaching one day or more classes in 2001.

Stephanie: What was the first class that you taught?

Barry: The first class that I taught was an "Introduction to Microbiology" for non-microbiologists.

Stephanie: In general, what does it take to prepare for a course?

Barry: A number of different areas must be examined before teaching is considered. These include having an interest and being curious about the topic, having an existing background in the topic area, perhaps having actually studied that area, a desire to perform additional research to learn about the topic and its current status in relationship to science, quality and U.S. FDA regulations. I also contact each student to determine what specific questions they may have and include these areas within the course presentation.

Stephanie: What do you discover as a course is being taught?

Barry: Courses are a very interactive activity where the attendees share their historical perspective, as well as their current views on their experiences. The students learn from each other as a result of this. I find myself acting as much as a facilitator as a presenter. I believe that the students learn more when there is class interaction opposed to when the lecturer only presents.

Stephanie: What is the teaching experience like?

Barry: I find the teaching experience extremely rewarding. I enjoy observing the students building on each other's experiences and find that they often add to my own.

Stephanie: Do students add their own input that help you to teach the course?

Barry: Yes, definitely. Not only do they add their own experiences, but when we have "break out" sessions, followed by their group reports, they amplify on the total experience of the class by offering their own personal case studies.

Stephanie: What do you get out of teaching?

Barry: I gain satisfaction from watching the students learn from each other. It's amazing how much the students can learn from each other in a lecture situation. However, the best learning situation is at the TRI facility in Bethesda where the students not only have lecture but also the ability to interact in both a laboratory and a clean room situation–the latter being an environment where most students would never be able to enter because of each company's gowning certification requirements. At the TRI facility, none of this certification is required since it is considered teaching and is not a "true" classified and controlled area.

Stephanie: What do you think students get out of it? What are other students' perspectives? What is your perspective?

Barry: I believe the students gain a greater appreciation of the subject matter that they never would achieve without the course, even if it is just through a lecture or it is a lecture, laboratory and clean room course. I find that the students remember the course contents and often will contact me–a week, a month, six months later asking for me to further explain a concept, a FDA requirement or a situation that we discussed in class.

Stephanie: How do you feel about winning the Agalloco award?

Barry: I was very surprised to learn that I had been nominated and won this award. I am quite honored to have received this award named to honor Jim and look to working with PDA in their educational programs for many future years.

About the Instructor

Barry A. Friedman, PhD is a Senior Consultant with Barry A. Friedman, PhD, LLC, a firm specializing in Regulatory Compliance, Aseptic Processing and Quality Control. Barry has been teaching on-site and public courses for nine years and for five years with PDA. He is the recipient of the 2010 James P. Agalloco award which is awarded to a PDA faculty member who exemplifies outstanding performance in education.

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www.pdatraining.org/cleaningval

14-15: Global Regulations and Standards: Influences on Cold Chain Distribution, Packaging Testing and Transport Systems
Bethesda, Maryland
www.pdatraining.org/coldchaincourse

28-30: Development of Pre-filled Syringes
Bethesda, Maryland
www.pdatraining.org/prefilled

May 2010

5-6: Integration of Risk Management into Quality Systems - Expanded
Bethesda, Maryland
www.pdatraining.org/Integration

5-7: Environmental Mycology Identification Workshop
Bethesda, Maryland
www.pdatraining.org/mycology

7: Achieving CGMP Compliance During Development of a Biotechnology Product
Bethesda, Maryland
www.pdatraining.org/achievingcgmp

11-12: An Introduction to Visual Inspection
Bethesda, Maryland
www.pdatraining.org/aivi

13-14: Choosing the "Right" Microbial Identification Program for Your Biopharmaceutical/Pharmaceutical Quality Control Laboratory (NEW DATE)
Bethesda, Maryland
www.pdatraining.org/microID

17-21: Aseptic Processing Training Program - Session 3
(Week 2: June 14-18) (SOLD OUT!)
Bethesda, Maryland
www.pdatraining.org/aseptic

19-20: PDA Vaccines Conference Courses
Bethesda, Maryland
www.pda.org/vaccines2010courses

Courses Include:
- Vaccines 101
- Uses of Bioassay for Vaccine Development and Product Control: Practical and Statistical Considerations
- Principles of Containment

24-26: Boston Course Series
Boston, Massachusetts
www.pdatraining.org/Boston

Courses Include:
- Sterile Pharmaceutical Dosage Forms: Basic Principles
- Risk-Based Analytical Method Validation – New Course
- What Every Biotech Startup Needs to Know about CMC Compliance
- Virus Clearance – New Course

June 2010

2-4: Developing a Moist Heat Sterilization Program within FDA Requirements
Bethesda, Maryland
www.pdatraining.org/DMHS

3-4: Elements of Risk Management
Bethesda, Maryland
www.pdatraining.org/elements

23-25: Fermentation/Cell Culture Technologies Training Workshop
Bethesda, Maryland
www.pdatraining.org/fermentation

July 2010

20-23: Downstream Processing: Separations, Purifications and Virus Removal
Bethesda, Maryland
www.pdatraining.org/downstream

26-30: Basic Microbiology for Aseptic Processes
Bethesda, Maryland
www.pdatraining.org/basicmicro

The PDA Training and Research Institute is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmaceutical education.

For more information on these and upcoming PDA TRI courses please visit **www.pdatraining.org**

* PDA's *Aseptic Processing Training Program* is not eligible for any discounts.

Container Closure Integrity Testing Methodologies

Alternatives to the Dye Test • Berlin, Germany • April 29 • www.pda.org/europe

Volker Eck, PhD, PDA

Container closure integrity is defined as the ability and quality of a container closure system to provide protection and maintain efficacy and sterility during the shelf life of a sterile drug product. The ability of rubber components to prevent microbial ingress of parenteral containers can be measured by seal integrity. To determine container closure integrity various testing methodologies are used. Some are for research and development purposes and help to characterize immediate container systems. Others are part of a sound control strategy and verify the constant performance of the manufacturing line during operation.

The most frequently used ones are:

- Helium Integrity
- Determination of Sealability (methylene blue dye filled vials)
- Determination of Self-Sealability
- Residual Seal Force
- Vacuum Retention Test

In practice, there are numerous types of container closure integrity test methods that are available with varying sensitivities. A helium leak test method is state of the art and there are conventional methods used by the industry for many years.

Helium Leak Testing

The most sensitive seal integrity testing technique uses helium leak detection. This technique offers advantages over conventional seal integrity methods. The system is based on a helium mass spectrometer leak detector equipped with custom fixtures for the particular vial or parenteral container to be tested. Such instruments can be calibrated against traceable standard leaks and measure the rate of helium leak from the container, as well as the actual percent of helium that is filled within the container. Various types of containers including vials, syringe systems, cartridges and blister packs can be evaluated.

By using the tracer helium gas technique, the leakages could be determined quantitatively. Published research [see Kirsch, et. al., PDA J. Pharm. Sci. & Tech., Vol. 51, pp. 195-207 (1997)] has demonstrated that a helium leak rate greater than 10^{-6} cm^3/sec can be considered a failure for closure integrity. Helium leak rates lower than 10^{-6} cm^3/sec have been associated with acceptable microbial challenge results. For sensitivity comparison, conventional seal integrity methods (i.e., dye leakage) have leak rates of 10^{-3} cm^3/sec.

Recommended applications of this technology include:

- General container closure integrity testing
- Seal integrity monitoring during stability studies
- Closure formulation/configuration selection
- Sealing machinery optimization/ validation
- Prediction of shelf life seal integrity
- Identifying the source of leaks

Conventional Methods

Conventional seal integrity test methods are widely accepted by the industry and regulators and are routinely used for research and development studies, problem solving and to generate baseline data. Basic testing methods include but are not limited to:

- Determination of sealability of rubber closures by methylene blue ingress
- Determination of the amount of vacuum within a sealed vial
- Residual seal force

The most common testing method uses methylene blue dye which after being filtered is placed into a vacuum vessel. Test samples filled with a suitable medium are then inserted into the vessel so that the samples are completely immersed in the dye. The vacuum vessel is then sealed and air is removed slowly. After a predefined length of time, the vacuum is slowly released. Samples then are removed from the vessel and cleaned to remove the dye. Samples are analyzed using either visual analysis or ultraviolet spectrophotometers. An aliquot from an untested sample is placed into a test tube. The detection limit is determined by adding a specific amount of dye to the untested sample until the dye is detectable visually or by the used instrumentation. Another aliquot is taken from an untested sample and transferred to a test tube to be used as the negative control. Aliquots from the contents of each sample are taken and place into a test tube, including a positive control. The negative control is compared to the test samples and the test tube used to determine the detection limit. Evidence of blue dye ingress is considered a failure.

Container Closure Integrity, Bacterial Immersion

This test is designed to evaluate the adequacy of the closure in maintaining a sterile barrier. Integrity maintenance is evaluated through liquid immersion of the containers containing sterile growth medium into a solution containing a microbial challenge, for example, Brevundimonas dimunta ATCC #19146, for a specified amount of time, pressure and vacuum. Containers are then removed from the challenge, rinsed, incubated and examined for growth. Again, controls are performed with each challenge, so it is common practice to prepare samples representing positive controls, negative controls and bacteriostasis controls. B. diminuta is an aerobic organism so it is recommended to allow for an air headspace of ≥50% of the total volume of the container in the test samples. The research by Kirsch et. al. cited above correlated physical leakage to microbiological barrier breakage.

Vacuum Retention Test

The vacuum decay leak test method consists of placing the test container in a chamber, sealing and evacuating the

chamber to a predetermined vacuum level, isolating the vacuum source and then monitoring the rise in pressure (vacuum decay) inside the chamber resulting from container leakage. This method would allow to test a complete batch for substantial leakage present. It is not as sensitive as the Helium Leak Test but some applications allow to test full batches. Vacuum decay's usefulness as a nondestructive leak test method for testing pharmaceutical packages has been recognized in published literature, as well as in compendium and recent U.S. Food and Drug Administration regulatory guidance.

The PDA Workshop, *Alternatives to the Dye Test* held on April 29 in Berlin, Germany, will address the question of what testing to be used under what circumstances, their advantages and limitations.

Relevant Documents:

- ASTM D4991
- ASTM F2338-09
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research, Center for Devices and Radiological Health, Center for Veterinary Medicine. *Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products*, Guidance for Industry, 2008
- Ph. Eur.: Chapter 3.2.9; *Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powders and for Freeze-Dried Powders*
- United States Pharmacopeia: <381> *Elastomeric Closures for Injection*
- United States Pharmacopeia: <1207> *Sterile Product Packaging—Integrity Evaluation*
- PDA Technical Report No. 27, (1998)
- Kirsch, et. al.; PDA J. Pharm. Sci. and Tech., Vol. 51, pp. 195-207 (1997)
- Kirsch, L.; Nguyen, L.; Kirsch, A.; Schmitt, G.; Koch, M.; Wertli, T.; Lehmann, M.; Schramm, G. ; PDA J. Pharm Sci. and Tech, Vol. 53, pp. 235–239 (1999)
- Heinz Wolf, Tony Stauffer, Shu-Chen Y. Chen, et al.; PDA J Pharm Sci and Tech, Vol. 63, pp. 472-488, (2009)
- Heinz Wolf, Tony Stauffer, Shu-Chen Y. Chen, et al.; PDA J Pharm Sci and Tech, Vol. 63, pp. 489-498, (2009)

Particle Monitoring in Aseptic Production Areas

Isolators, RABS and Clean Rooms – Advanced Technologies and Trends • Basel, Switzerland • June 8-9 • www.pda.org/europe

Volker Eck, PhD, PDA

The last PDA Conference on Pharmaceutical Microbiology saw a fascinating lecture from **Berit Reinmueller**, PhD, and **Bengt Ljungqvist**, PhD, on particle counting issues in aseptic manufacturing areas. In essence, one problem they made everybody aware of was the intrinsic limitations of some particle counting equipment. Their claim was that there several issues around particle samplers.

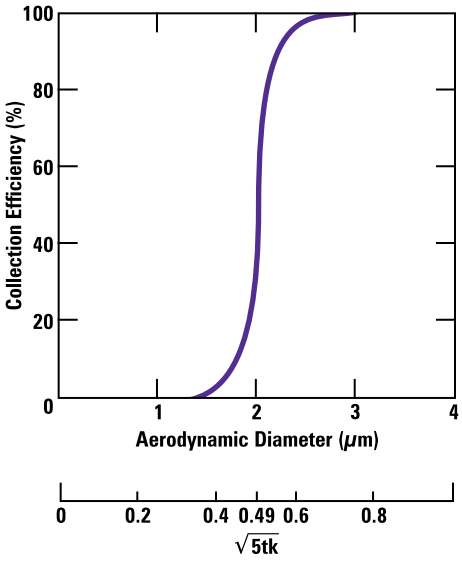
First, physical extraction efficacy is related to the geometric design of the sampler like:

- Size of inlet
- Direction of inlet
- Design of inlet
- Capture region

These parameters will determine if a given equipment was a suitable apparatus if used to collect viable contaminants by impaction. Any contaminant could either be cut off because it was not drawn into the sampling device, moved out of the sampler by the jet stream or it was captured on the impaction plate. The cut off characteristic determining this is the aerodynamic particle diameter, also called equivalent particle diameter, which describes a unit density sphere having the same settling velocity as the particle studied. The d_{50} value would define the aerodynamic particle size diameter (in µm) of contaminants collected with 50% efficacy (See **Figure 1**). Using well known correlations, for example, the theoretical particle separation for a slit impaction sampler using a sampling air flow of 50 L/min and equipped with a slit of 1mm X 25 mm, thus having an impaction velocity of 33.3 m/s and a d_{50} value of 1.55 µm.

Using the same correlation, however, a sieve impaction sampler with 12 holes of 10 mm diameter each would have a larger hydraulic diameter of the inlet opening and by applying a higher sampling air flow of 100 L/min would impact the

Figure 1: The relation between efficiency in capturing and the diameter and highlights the d(50) value



velocity of 1.8 m/s and would only result in a d_{50} value of 14.8 µm (See **Figure 2**). Under such circumstances it can be expected that the latter would show a much lower recovery rate. Experimental data shown gave evidence to this conclusion demonstrating that in all 12 runs executed, the slit impaction sampler showed a significant higher collection and recovery of microbial contaminants than the sieve sampler.

In another experiment, they could show that by reducing the cut off size from a d_{50} value of 7.9 µm to a d_{50} value of 0.3 µm the contamination recovered increased from 33 CFU/m³ to 92 CFU/m³ (See **Table 1**).

Their general conclusion of these results was that different measuring principles and different sampling equipment designs lead to different detection levels. This is inherent and cannot be avoided. However, it is wise to consider such limitations when performing a risk assessment for any environmental monitoring program.

The fact is that a trend of zero contaminants does not indicate that there were no contaminants at all. The issue of particle measurement and monitoring will be in the centre of a future PDA conference on *Isolators, RABS and Clean Rooms –*

Figure 2: The difference in capturing viable contaminants for the split (clear) and the sieve (red) sampler

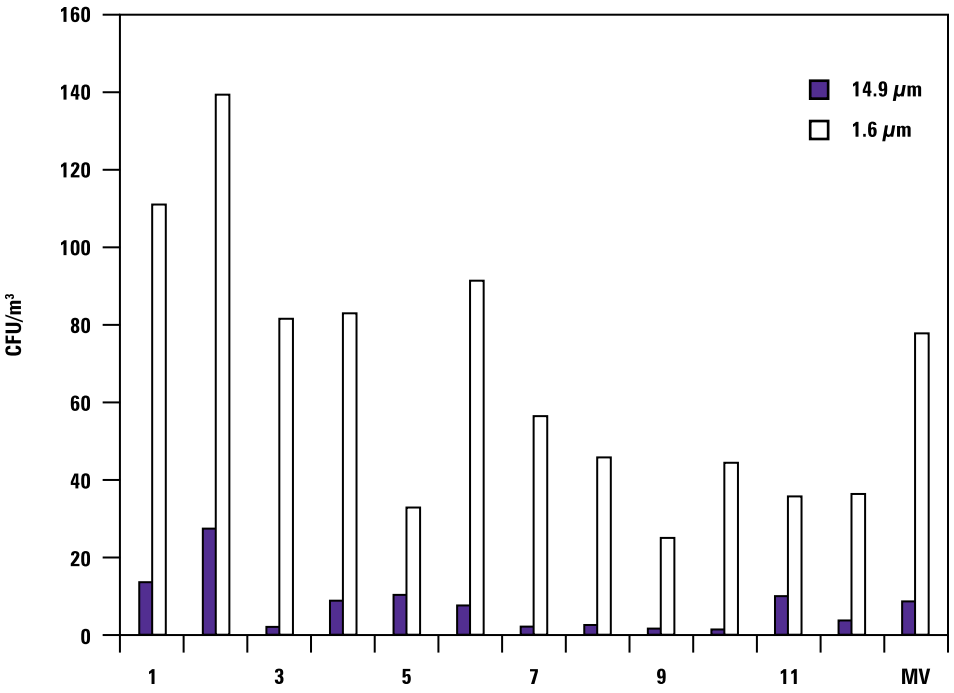


Table 1: The increase of viable contaminants found when the d(50) value decreases

Number of CFU per Plate(s)		Cutoff Size (μm) d_{50}	Number CFU/m³
Plate 1	19	7.9	33
Plate 1+2	26	5.1	46
1+2+3	32	3.6	55
1+2+3+4	37	2.5	65
1+2+3+4+5	45	1.0	79
All 6 plates	53	0.3	92

Advanced Technologies and Trends on June 8 -9 in Basel, Switzerland.

This conference and its adjacent companion *Innovative Aseptic Technologies* which will be held June 10-11 in Basel, Switzerland will provide a broad overview on recent developments. They will illustrate how to define control strategies that allow to improve product quality. At the same time, experts and participants will also discuss critical process elements and procedures that ultimately impact on sterility assurance levels. Both events present an important occasion to get to know and compare technological solutions and selection strategies for who is involved in or responsible for aseptic manufacturing.

Interested professionals are advised to mark this date and plan to attend. More information can be found at www.pda.org/europe.

PDA's Who's Who

Bengt Ljungqvist, PhD, Professor, Kungi Tekniska Hogskolan, Royal University of Technology

Berit Reinmueller, PhD, Senior Research Engineer, Kungi Tekniska Hogskolan, Royal University of Technology

PDA Parenteral Drug Association *Connecting People, Science and Regulation®*

PDA Europe Upcoming Conferences October 2010

Visual Inspection Forum

Visual inspection continues to be an important element of the manufacturing process and the quality assurance of injectable products. Product inspection provides necessary information for lot release, and, coupled with defect identification, contributes to a strategy of continuous process improvement. The meeting will provide a forum to present and discuss new developments in the field of visual inspection, including a basic understanding of the sampling and inspection process, validation of manual and automated methods and the regulatory and compendial requirements that govern them. Special attention will be given to specific inspection challenges of biopharmaceutical drugs e.g. turbid media as well as the differentiation between protein aggregates and foreign particles.

5-6 October 2010
Berlin/Germany

Conference, Exhibition: 5-6 October
Training Course: 7-8 October

Pharmaceutical Cold Chain Management

Temperature Controlled Pharmaceutical Supply Chain - From Manufacturing to the End User

The 2010 PDA two day event will focus on the supply chain of temperature controlled pharmaceuticals from the manufacturer to the end user. Aspects of temperature controlled qualification and validation using new technologies will be presented. Distribution stability studies and shipping outside of label claim will be debated. A special session is planned on storage and transportation solutions for ambient, refrigerated and frozen products. Wholesalers and pharmacists will be invited to present their plans and systems for Quality Agreements, temperature alarms and distribution traceability. The attendees will hear from regulators, industry experts, and cold chain solution partners about risk management for temperature controlled supply chain.

The 2010 **NEW** two day Cold Chain Training will consist of 4 modules covering (1) Global regulatory requirements including an overview of the recently published PDA Technical Report No. 46, Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User, (2) Packaging Development, (3) Temperature Monitoring and Data Analysis, (4) Cold Chain Risk Management. All concepts will be clarified by round table discussions and case studies.

7-8 October 2010
Berlin/Germany

Conference, Exhibition: 7-8 October
New Training Course: 5-6 October

For other events see:
www.pda.org/europe

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