

A visible player in the development of FDA's 2011 Final Guidance on Process Validation, Grace McNally shares her experience on the effort it takes to shape such policy and her perspective on the Guide's key recommendations.

PHARMACEUTICAL ENGINEERING Interviews

Grace McNally, Senior Policy Advisor, FDA CDER Office of Compliance, Division of Manufacturing and Product Quality

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Grace McNally is a Senior Policy Advisor in CDER's Office of Compliance, Division of Manufacturing and Product Quality, Guidance and Policy Team. She is active on several working groups dealing with process validation, combina-

tion products and revisions of the CGMPs, as well as developing training for FDA and industry. She has served as Compliance Officer handling CGMP cases and as a field Investigator in ORA (Office of Regulatory Affairs) specializing in drug and medical device inspections. Prior to coming to CDER she worked in Denver District and Philadelphia District. She graduated from Boston College, Chestnut Hill, MA.

Q Can you please give us an overview of your role and responsibilities as Senior Policy Advisor in CDER's Office of Compliance, Division of Manufacturing and Product Quality, Guidance Policy Team?

A The Guidance and Policy (GAP) team manages the development of regulations, enforcement policy, guides/inspection programs and guidance for industry related to drug CGMPs and other adulteration issues. Additionally,

GAP members consult on cases under review by our pre-approval, domestic and foreign case management branches, develop ORA inspection guides, provide input on ORA training courses, and comment on external documents impacting drug quality (e.g., USP, ISPE, PDA, and PIC/S). Other responsibilities include managing division procedures, coordinating responses to external inquiries, and providing input on international agreements impacting on surveillance and enforcement of drug quality.

My responsibilities within the GAP team include developing guidance for industry, participating in the Combination Product workgroup and the CGMP regulation revision workgroup, and developing training courses/materials for FDA investigators and DMPQ personnel. Also, I provide CGMP case consultations to Division compliance officers and field personnel. I am the Division's representative on a couple industry committees and advisory boards. I chaired the workgroups that developed the process validation guidance. Since its publication in January 2011, industry outreach and internal FDA training associated with the final PV Guidance for Industry has been a focus.

Q Process Validation is a hot topic for ISPE Members and the pharmaceutical manufacturing industry in general. What was your direct involvement in the final *Guidance for Industry – Process Validation: General Principles and Practices*?

AI was Chair of the original and revision working group. CDER Office of Compliance led this effort which was initiated as part of the CGMPs for the 21st Century initiative. One workgroup created the original 2008 draft, and a second one convened to finalize it based on comments to the draft. Many of the original members were on the second workgroup but we also benefited from new members and their fresh perspectives.

I led meetings, drafted language, helped edit text, and facilitated discussions to resolve differing opinions and keep us moving forward. I also handled the administrative tasks, e.g., create agendas, maintain document versions, and summarize progress. The drafting was truly a group effort; my colleagues from CBER, CVM, ORA and other Offices (Pharmaceutical Science, Generic Drugs and Biotechnology Products) were excellent contributors. I also had great support from my colleagues in Office of Compliance. Brian Hasselbalch, GAP Team Leader, initially co-chair, continued to participate and provide input through to the completion of the project. Two Compliance Officers (Tamara Felton and Steve Hertz) and one of our Regulatory Counsels (Paula Katz) in Office of Compliance also were enormously helpful in organizing and summarizing the comments from the 2008 draft and editing the final version. The Division Director, Rick Friedman, stayed informed and was very supportive.

QDo you believe the guidance's recommendations will change industry's approach to process validation in general? If yes, how? If no, why not?

AYes, I do. This guidance reinforces several foundational principles of the CGMP regulation essential to long term process validation success. First, this guidance advocates "lifecycle" thinking as opposed to a "once and done" process validation mentality. Lifecycle thinking fosters better planning and knowledge management and incorporates feedback for process improvement.

Secondly, this guidance highlights process design, including understanding process parameter and material attribute interactions, as part of the lifecycle. Good design work increases the odds of a successful commercial scale qualification and robust process overall.

And, finally, the lifecycle comes full circle in Stage 3 which reflects in part the requirement in 211.180(e) which obligates manufacturers to periodically evaluate their manufacturing experience and determine the need for changes. The recommendations about measuring process performance and process variability with statistical tools and data analyses are directly related to several key CGMP requirements, e.g., 21 CFR § 211.110(a), 211.110(b), 211.165(d).

I think the guidance will cause manufacturers to rethink a "one-size-fits" all PV approach. This guidance promotes scientific and risk-based approaches that incorporate, rather than overlook, the different or unique aspects of the particular product and process under study. Ultimately, routine oversight should be aligned with the normal behavior of the process in order to detect shifts or drifts, etc. The root cause of any unexpected behaviors will likely be easier to determine because of the greater degree of process knowledge.

QFrom your experience working on the Guidance, what challenges did the FDA face in developing the Guidance?

AThe workgroup members had different regulatory responsibilities, scientific backgrounds, and industry experience. Initially, our diverse backgrounds were challenging but ultimately proved to be our greatest strength. Over the course of our collaboration, we gained broader insight into the inspectional, review and compliance issues surrounding process validation. We had to consider the differences in statute and regulation, as well as any historical conventions, between the different drug types covered by the Guidance. The diversity of the workgroups

made for productive discussions about these issues and contributed greatly to the strength and scientific standing of the principles and recommendations in this Guidance. I learned a great deal and have tremendous respect for my colleagues with whom I worked on this project.

QWhat do you think were the main concerns industry voiced from the 2008 draft of the Process Validation Guidance and how are those concerns addressed in the final version?

AWe received comments concerning applicability of the Guidance to legacy products and processes, and also issues surrounding statistical sampling, statistical data analysis and measures of process performance.

Regarding legacy processes, the final version includes some clarifying language stating that implementation of the recommendations of the Guidance would likely begin in Stage 3. The programs manufacturers already have (or should have) to collect and analyze product and process data can be used to evaluate the state of control of the process. These evaluations may trigger a return to some of the activities described in Stages 1 and 2.

From a lifecycle perspective, validation is an ongoing activity and manufacturers should establish a program(s) that regularly assesses the state of control regardless of when or how the process was developed. Changes to correct or improve the process and control strategy should be proactively pursued as increasing process knowledge and experience dictates.

The industry also expressed concern about the emphasis on statistics – applying statistical tools, metrics and analyses to manufacturing data, and objectively measuring the performance of their processes. The gist of the concern was mostly where and how to begin implementation rather than objections to the need for it. I believe there is recognition that the CGMPs have long required this.

During conferences and other interactions with industry, I am hearing

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that some industry groups, individual companies and consultants are initiating task forces or committees, internal projects, or writing papers to share ideas and information about this topic. This is very encouraging.

The use of statistics is not a new discipline or field of study. Many resources are available in the literature and manufacturers need to move forward in this area. I am hopeful this will lead to more meaningful studies and criteria during Stages 1 and 2 as well as more targeted and value added Stage 3 programs.

Consumers expect the drug to have the same quality every time they ingest, inject or apply it. This Guidance is promoting better measurement of intra-lot and lot-to-lot consistency. The appropriate level and frequency of routine sampling and monitoring should be tied to that knowledge.

Q You delivered a presentation on the Guidance at ISPE’s Tampa Conference in February. Considering the 2008 draft release was met with mixed reviews and interpretations, Tampa Conference audience members were relatively quiet and had few follow-up questions. What is your opinion on how the final Guidance has been received by industry?

A My Office has received positive feedback. Many welcome the emphasis on a scientific, well reasoned approach to design, demonstration at commercial scale, and monitoring and maintenance in accordance with some reasonable and measurable confidence.

The Guidance also created some anxiety. While some saw the opportunities and value added, others felt concern about losing what they perceived as ‘certainty’ in PV expectations. People

naturally seek standards, and uniform approaches in the interest of efficiency and regulatory certainty. The agency supports that if the science is there for the product/process in question. In our past experience we saw (and, disturbingly, still do) more than a few instances where design work and process understanding was minimal, qualification efforts were rote and devoid of truly meaningful acceptance criteria and a thoughtful, scientific process monitoring program(s) was altogether missing.

This guidance emphasizes the necessity of comprehensive design work, meaningful process performance criteria, data collection and analysis, and a solid process monitoring program.

Q What is a main takeaway message from the Guidance you feel could serve as a beacon to industry as it considers and implements concepts within the Guidance?

A Seek to understand, in a methodical, scientific way, the interactions between process parameters and raw material attributes. Understand their impact on the important safety, efficacy, and quality attributes of the drug. For the initial qualification, build a scientific and comprehensive approach around those key aspects. Past protocol(s) may or may not be appropriate for the new product/process under study. Consider its uniqueness first; then consider if existing platforms or approaches make sense for this new process.

Q Is there a coordinated global effort between agencies to align the process validation/requirements/regulations? If so, what is your role in this?

A FDA has been involved in international harmonization efforts on a variety of issues. The ICH collaboration is a well-known example. However, a formal initiative to globally align process validation requirements is not underway at this time. Nevertheless, during meetings or other occasions where FDA and other regulators convene, the issue is being discussed. Through these discussions in which several of my colleagues and I participate, we hope to better understand the various perspectives and share ours as well. This may lead to a coordinated effort in the future.

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

A Outsourcing and the increasing globalization of the industry are the biggest changes I’ve witnessed in my career. A move from all-under-one-roof to a contracting environment may bring industry greater efficiency but also creates new challenges. For example, separation of process design and development from the commercial manufacturing site may raise some difficult issues regarding the process and product knowledge. Those parties who are qualifying and maintaining the process need access to certain information and knowledge. Companies will need to examine their knowledge sharing practices with contractors and their quality agreements. I expect there will be an emphasis on figuring this out in the next few years. 