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EDITOR’s NOTE: Welcome to IPQ’s “Monthly Update” on key CMC/GMP developments in the US, Europe, and internationally. The IPQ family of publications includes “The News in Depth” and “Updates in Brief” on our website as they occur, “Weekly News Alerts” sent via e-mail, and the “Monthly Update.” IPQ’s suite of offerings support our mission of helping readers understand, engage in and respond to the dialogue and developments around evolving and harmonizing the regulation of drug and biologic quality and manufacturing. Subscribers and license holders to IPQ have access to all of these sources of cutting-edge news and in-depth analysis as well as to the full IPQ archives. Visit IPQpubs.com for further information.

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FDA’s Draft ANDA Stability Guidance Applies ICH Expectations to Generics

The Office of Generic Drugs (OGD) has released a new draft guidance indicating that Abbreviated New Drug Applications (ANDAs) and the Drug Master Files (DMFs) that support them will be expected to follow the stability recommendations provided in the ICH Q1A-E stability guidelines.

The content of the guidance is only two pages. A short introduction and a background section, which lists the ICH QA-E guidelines, are followed by a discussion section that tells the applicant how to apply the ICH stability recommendations in the drug substance and product context.

When following the ICH stability recommendations, the draft guidance states, the applicant should:

- Submit data from three pilot scale batches or two pilot batches and one small scale batch. If the size of the pilot does not follow ICH recommendations, the applicant should provide a justification.
- At the time of submission, provide 6 months of data that include accelerated and long-term conditions. FDA recommends following ICH with respect to utilization of intermediate conditions to support shelf-life.
- Use multiple lots of drug substance as appropriate.
- Manufacture and package the drug product using principles that are representative of the commercial process.

- Provide a fully packaged primary exhibit batch.
- Use three batches when bracketing and matrixing designs under ICH Q1D.
- Provide statistical analysis of the data as appropriate, in accordance with ICH Q1E, Appendix A.

Applicants deviating from the recommended procedures should justify the approach they are taking, OGD indicates.

The office had met with representatives of the Generic Pharmaceutical Association (GPhA) for input during the guidance drafting process and will be looking for further input from stakeholders during a comment period that will extend for three months following the draft’s publication in the Federal Register.

Draft Reflects Industry Input

At the GPhA/FDA CMC workshop in May, OGD Senior Review Chemist Raman Murali previewed the draft guidance and described the context and reasons for his office more formally adopting the ICH stability standards (see IPQ “Monthly Update” September 2012, p. 32) – Murali’s full remarks are included in the story).

Murali explained how the move fits in with OGD’s overall effort to better align its ANDA standards with those for new drugs and internationally, in line with the new quality-by-design paradigm.

Also addressing the May workshop was a member of the GPhA stability subcommittee, Nicholas
Cappuccino, who discussed his group’s concerns and recommendations regarding the application of ICH Q1A (stability testing), Q1D (bracketing and matrixing) and Q1E (stability evaluation) to generic drug products (see IPQ “Monthly Update” September 2012, p. 32)

Cappuccino participated on the ICH working group that wrote Q1A and, as such, has provided salient background information and expertise to the GPhA committee.

While some further refinements and clarifications may be needed in applying the innovator-oriented ICH standards to generics, he said, “from my point of view, we are not very far apart from where we need to be to bring this forward in a very cooperative way.”

The draft does allow for six months of stability data at the time of ANDA submission and provide for matrixing and bracketing, as urged by the GPhA subcommittee.

Other of the GPhA concerns, such as the implications of minor formulation changes from the innovator product, expiration dating, and where the packaging for the exhibit batch is performed, are not specifically addressed in the draft guidance.

The industry/regulator dialogue on the efforts underway to improve FDA’s generic drug review process, including those related to stability, will continue at the GPhA/FDA Fall Technical Conference in Bethesda, Maryland on October 1-3, which, like the spring workshop, is sold out.

The keynote address for the Fall conference will be given by the new OGD Director, Gregory Geba, who took over the helm in July (see IPQ “Monthly Update” September 2012, p. 58).

A significant portion of the meeting will be focused on GDUFA implementation issues, including their impact on industry and the regulatory process. Biosimilar technical issues (see IPQ “Monthly Update” July/August 2012) and the industry/FDA collaboration on drug shortages (see IPQ “Monthly Update” February 2012, p. 9) are among the other issues that will elicit FDA and industry discussion.

IPQ has been closely tracking FDA’s broad-ranging efforts to create a more efficient and effective generic drug review process, including the initiative on stability. Building on a foundation of QbD and user fees, the efforts are intended to address an expanded backlog of ANDAs and fulfill OGD’s commitments to industry under the Generic Drug User Fee Amendments (GDUFA). See IPQ’s September 2012 Monthly Update.

DOWNLOAD FROM THE STORY:
• ANDA stability draft guidance document

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FDASIA Title VII Empowers FDA in Supply Chain Arena; Congress Adds Other Tools to Help on Drug Shortages and Theft

Title VII of the Food and Drug Administration Safety and Innovation Act (FDASIA) gives FDA additional tools it has been seeking to better confront the challenges of regulating a global supply chain.

While the sections of FDASIA on user fees and their expansion into generics (Title III) and biosimilars (Title IV) have been garnering front-burner attention (see IPQ “Monthly Update” September 2012), agency officials at recent public meetings have also been emphasizing the importance and potential impact of the new supply chain-oriented provisions in Title VII.

At the National Press Club on September 28 in Washington, DC, FDA Commissioner Margaret Hamburg emphasized that the passage of FDASIA is “perhaps the most important development” in the past two years regarding safety of the drug supply chain and combating counterfeiting.

At a Global Outsourcing Conference sponsored by Xavier University and FDA in late September, OMPQ Director Steven Lynn commented that FDASIA “is going to help us a great deal. It isn’t everything, but it is a lot more than we had before.”

The authorities under which FDA has been working under are “antiquated,” he stressed, and cannot address “the challenges faced by this ever-changing global environment.” FDASIA was passed, Lynn explained, to address this situation.

Of the eleven sections in the 140-page law, Title VII is viewed as particularly transformative in giving FDA mechanisms to better understand and counter the threats posed by counterfeiting, adulteration and subpar foreign manufacturing practices.

Although the law formally became effective on October 1, most of the significant provisions will not be put into place until FDA has promulgated regulations and guidance to flesh out how the provisions will be implemented.

Title VII provides for:

- a modernized facility registration system for both foreign and domestic manufacturers
- a risk-based approach to determining which and when foreign and domestic manufacturers need to be inspected
- supplier inclusion in quality systems as CGMP
- using inspection results of trusted foreign regulators to help FDA decide on where to target its limited inspection resources
- foreign companies having to show that their products meet the FD&C Act requirements as a condition of sale in the US
- manufacturers and wholesalers reporting drug thefts and counterfeits to the agency
- greatly enhanced criminal and monetary penalties for counterfeiters and adulterers
- penalties for foreign manufacturers that refuse or delay FDA inspections
- FDA destroying adulterated or misbranded imported drugs rather than returning them, and
- guidelines that will allow sharing of trade secret information with foreign regulators.

FDASIA also includes provisions specific to the drug shortage component of the supply chain equation in its Title X. This section calls for enhanced reporting requirements on shortages and potential shortages and the creation of a task force to look at the appropriate measures to detect in advance and mitigate drug shortages.

As a follow-up to FDASIA, Congress has also cleared the Strengthening and Focusing Enforcement to Deter Organized Stealing and Enhance Safety Act, or “SAFE DOSES Act,” which includes increased penalties for large-scale theft of pre-retail drugs, providing FDA with another weapon in its supply chain arsenal. The Senate passed the legislation in early October, and it is now awaiting the President’s signature.

Title VII Has Three Buckets

At the Generic Pharmaceutical Association (GPhA) Fall Technical Conference in Bethesda, MD in early October, Office of Compliance Acting Director Ilisa Bernstein provided an overview of the FDASIA legislation, focusing in particular on its supply chain provisions.

Bernstein pointed out that the new authorities in Title VII could be broken up into three “buckets” (see box on p. 5).

“One is providing new risk information about: what facilities are out there; what they are doing; how to get
Bernstein also highlighted the importance of new authorities to detain products, institute higher penalties for intentional adulteration and counterfeiting, and institute extraterritorial jurisdiction that gives the agency “better ability to reach outside the US when there are problems.”

**Congressional Staffers Provide Insight**

At a Global Outsourcing Conference (GOC) co-sponsored by Xavier University and FDA in late September in Cincinnati, Ohio, two Congressional staffers who were instrumental in the development and passage of FDASIA took a deeper dive into several of the key provisions in Title VII and their intent.

Representing the House was Kim Trzeciak, legislative director for Congressman John Dingell (D-MI), one of the key sponsors of the legislation. Trzeciak played an active role in the House Committee on Energy and Commerce negotiations with industry on user fees.

Representing the Senate was William McConagha, health policy advisor to Senator Tom Harkin (D-IA) who chairs the Senate Health, Education, Labor and Pensions (HELP) committee. McConagha is on detail to the committee from FDA, where he has served in the Office of the Chief Counsel and as an assistant commissioner for policy.

In addition to providing explanations of the various provisions of Title VII, the staffers addressed the need for regulations and guidance to be promulgated by FDA for the provisions to take effect.

Trzeciak explained that one of the first actions the agency will need to take is issuing guidance on what will constitute a “delay, denial or limitation” of an inspection.

Beginning in January 2014, regulations will need to be promulgated on:

- importer standards and what documentation will be needed to allow products to be introduced into the US
- due process and testimony related to administrative destruction and detention,
- good importer practices.

A regulation will also be required to effectuate the increased admissibility standards required in section 713. Congress gave FDA a lot of discretion in promulgating the regulations to determine exactly what sorts of evidence would be necessary to be presented at the borders as a condition of entry.

McConagha explained that although the section on FDA agreements with foreign governments to share information does not necessarily need a guidance or rule-making, it will require negotiation. The bill spells out requirements that the agency will have to meet in executing those agreements, and Congress would like to see the agreements developed more information from foreign regulators; knowing about commercial importers; and requiring manufacturers to provide us notification when there is a theft or a counterfeit.”

In another bucket are provisions directed at the global supply chain, including a more risk-based inspection approach and pre-inspection record availability.

“We can now ask before doing an inspection for information that will help us target the inspection or even decide whether we need to do there right now,” Bernstein commented. “These are actually important new authorities that that not only help us but help you.”

On the provision for a risk-based inspection approach, she pointed out that it represents a move away from the current rule, which only recognizes the need for domestic facility inspections on a two-year basis and does not mention foreign facilities.

**Bernstein highlighted in particular the recognition in FDASIA that the extension of a pharma quality system across the supply chain is now CGMP. “This is something that we were really excited about getting,” Bernstein commented.**

A third bucket of the Act involves enhanced tools “for ensuring products that are marketed or offered for import into the US are compliant products. It gives us new ability to destroy products at the border and to deny import if an inspection is delayed, limited, or we were refused inspection, so that those products can’t be imported.”
promptly.

**New Facility Registration System Creates Parity**

Among the FDASIA provisions is the creation of a facility registration system that will apply to both foreign and domestic manufacturers and require a unique facility identifier.

Under the provision, domestic and foreign drug manufacturing facilities will be required to register annually with FDA between October and December. In addition to the unique facility identifier, a point-of-contact email will also be required.

“The goal here,” Trzeciak stressed, “is to make sure that FDA is getting the information they need regarding who is manufacturing and where in a timely and concise manner.” Also covered for the first time will be commercial importers.

“For a long time, importers have come in and out of the market with no knowledge by the FDA,” she said. “By having them register annually, not only will FDA establish a relationship with those that are importing drugs into the United States, but they will actually know who they are and where they are located.”

**Inspection Frequency Will Be Risk-Based**

Under FDASIA, the timing of both foreign and domestic inspections will be based on a risk analysis rather than a prescribed frequency, allowing greater inspection parity and better targeting of agency resources.

The Act calls for the risk-based inspection schedule to be based on a number of different factors, including: ● compliance history ● history and the nature of any recalls ● the risk of the drug product that is being manufactured, and ● inspection frequency and history, including whether that facility has been inspected within the last four years, as well as any inspection history by a foreign government.

The goal of this particular provision, Trzeciak said, is to make sure that there is inspection parity between domestic and foreign manufacturers. The intent is also to “ensure that FDA can target its resources where they are needed the most – making sure they are going to facilities that need inspections more frequently, and making sure they are targeting facilities that have a history of manufacturing problems.”

While more could have been done to increase the inspection parity, “this will be a nice start,” she commented. FDA will report to Congress on the inspections that they are doing based on this risk-based inspection schedule “so that we will be able to see if it has the true intent that we wanted to accomplish.”

McConagha added that there was a lot of discussion regarding whether to require a minimum frequency of inspections both domestically and abroad. However, there was a realization that doing so would have required large sums of money to be appropriated to FDA – something that Congress in the current environment is unable to do.

At the GPhA conference, Bernstein explained that the risk-based inspection provision in FDASIA codified practices already in place at the agency – something that is not unusual in Congressional legislation and applies elsewhere in FDASIA.

The law lists a number of risk-based criteria for FDA to consider, she pointed out. “But we have been doing risk-based approaches in the Office of Compliance for some time now. Our GMP site selection model, in terms of how we identify where we are going to go for surveillance inspections is a risk-based approach. How we do sampling and testing in the marketplace or at the border is a risk-based approach” (see IPQ “Monthly Update” April 2012, p. 25).

She added that the agency is “also looking at doing a better job at trending and analyzing the field alert reports that are coming and how those can feed into our risk-based approach as well – information that we can capture better that can help us figure out where the highest risks are.”

As part of its effort to upgrade its FARs program, in late September the agency announced a pilot that will provide for secure electronic submission of the reports, simultaneous transmittal to the appropriate district office and the Center for Drug Evaluation and Research (CDER), and unique identifiers for each report (see the story on p. 14).

**CGMPs Now Cover Supplier Relationships**

FDASIA’s quality management system provision in section 711 extends a drug manufacturer’s QMS to its suppliers, ensuring that the risks each share are managed together.

“The goal here was to make sure that manufacturers are establishing relationships with their suppliers,” Trzeciak commented. The relationship begins with manufacturers auditing suppliers before they enter into agreements with them.

The FDASIA provision requires that “quality management controls” are included as part of CGMPs. The controls are aimed at ensuring that manufacturers and their suppliers are managing the risks to their ingredients and to their finished drug products – that they are overseeing risk assessments
and they know where the risks lie.

The intent, Trzeciak pointed out, “is to put into place what good, responsible manufacturers are already doing and make sure it is part of something that they are doing as they are manufacturing throughout the supply chain.”

Alston and Bird Partner Cathy Burgess, who was involved in the formative GMP-related Barr Labs case as defense counsel, echoed Bernstein and Trzeciak on the importance of the Section 711 provision during a presentation she gave on preapproval inspection (PAI) readiness at an “FDA Inspections Summit” sponsored by FDANews in September in Bethesda, MD.

It means that “you could be out of compliance with current good manufacturing practices if you have not established adequate controls of your raw materials and your components,” she explained, noting that “this is the first time that this wording has existed in a statute.”

The substance of the provision has existed on the device side under the purchasing control standards in 820. “FDA has sort of gotten around that on the drug side, but never with a statute to back them up,” the Allston and Bird attorney said.

The result, she cautioned the pharma industry audience, is that “you are going to see more and more” attention to supplier management in the drug compliance arena.

Heparin, Burgess said, “was a wakeup call for FDA. As the global supply chain got longer and longer and more complex, people were not really paying attention to what was going on throughout the supply chain.”

She cited the FDA findings in 2010 at the Chinese API manufacturer Nanjing as an example of “the things you need to be aware of.” As documented in a subsequent warning letter, Nanjing had made a practice of scrapping off the data from its batch records (see IPQ “Monthly Update” May 2011, p. 11).

FDA visited Nanjing to inspect its production of an animal drug awaiting approval. The seriousness of the findings, however, led the agency to do a full GMP inspection across its API production.

“If you have an application,” Burgess stressed, “you know you are potentially going to have a PAI. You need to make sure you have a robust supplier management program, and you need to really check up on your suppliers.”

Partnering with Burgess in the PAI presentation at the inspections conference, Olson Frank Weeda Principle Attorney Fred Branding, a former Civil Division Chief at the Illinois US Attorney’s Office, also referenced Nanjing as an example of the attention firms need to pay to foreign suppliers.

Branding stressed that the results of such inspection findings include the withholding of application approval and the issuing of an import alert. He noted that the import alert can be placed on a product that appears to be adulterated or misbranded – “a very low standard to stop a product from coming into the market. And it is a very powerful administrative tool – FDA does not have to go to court to do that.”

Leverage Foreign Agencies’ Inspection Reports

Sections 710 and 712 of FDASIA explicitly authorize FDA to enter into agreements with foreign governments to exchange information about inspections, including foreign inspections of facilities that sell drugs into the US and FDA inspections of firms that sell abroad.

Section 712 further authorizes the agency to rely on the foreign inspections to help inform its own use of resources and to help inform its own assessment of where risks lie. In concert with the risk-based inspection approach, the agency will need to exercise judgment to choose where to devote its limited inspectional resources, McConagha commented.

In looking at foreign inspection results, he explained, the agency may have a better sense of those firms that appear, by virtue of passing, for example, an inspection by a European agency, to be low risk and not the sorts of firms that the agency needs to inspect. FDA could then devote its resources to the inspection of foreign facilities that either no trusted ally has ever seen, or to those where other regulators have found problems.

The provision builds on the premise that in a global supply chain, when all governments have limited resources, it is important to maximize cooperation, McConagha said.

Imported Products Must Prove Compliance

FDASIA introduces a requirement that foreign companies demonstrate that their products meet the FD&C Act provisions as a condition of sale in the US. Previously, the burden fell on FDA to prove that products were unsafe to disallow importation.

The demonstration may range from the integrity of the product labeling to the integrity of the manufacturing process, or anything else that may bear on the safety or effectiveness of the drug product, McConagha explained.

He pointed out that in much of the regulated world...
Report Counterfeiting and Thefts

A “notification” provision in FDASIA section 715 will require manufacturers and wholesalers to report to FDA “a significant loss or known theft” of drugs intended for the US market as well as any known instances of counterfeit drugs that are or “could reasonably be expected to be” for sale in the US.

The provision was prompted in part by instances in the past few years of major pharmaceutical warehouses being broken into and large volumes of drugs being stolen and diverted (IPQ “Monthly Update” April 2012, p. 22 and October 2010, p. 15). Some then worked their way back into the system clandestinely without any clear sense of how those products have been handled from the time of their theft to the time that they appear on retail druggist shelves.

Notification of thefts to FDA will allow the agency to assist in the investigation into the criminal wrongdoing and to better monitor the domestic drug supply.

There is also a requirement that wholesale distributors or manufacturers notify FDA in instances where there is reason to believe that a counterfeit drug product has been introduced into the US drug supply, or if it has been counterfeited abroad and there is reason to believe that it will be introduced into the US.

Congress realized that if major pharmaceutical manufacturers were required to notify the agency every time they identified a counterfeit product abroad, McConagha explained, there would be an endless number of submissions of information, many of which may not be particularly material. As a result, the provision was targeted specifically at addressing the identification of counterfeit products that appear to be being offered for sale or sent into the US system, so that there could be an effort to interdict those drugs and prosecute the counterfeiters.

To help attack the growing warehouse and cargo theft problem, in early October the US Senate passed the “SAFE DOSES Act,” which greatly increases the penalties for theft, transportation and storage of medical product cargo.

The new penalties provide for up to $1 million in fines and up to 30 years in federal prison upon conviction. The maximum penalties will be sought for “aggravated offenses” – those in which the theft is committed by an employee in the supply chain or serious injury or death results from the use of the stolen product.

Instrumental in introducing the bill was a team of pharma industry officials led by Johnson and Johnson, as well as members from the Pharmaceutical Security Institute (PSI), Pharmaceutical Supply Chain Security (PCSC) and other industry groups.

Counterfeiting Penalties Increased

Under FDASIA, the felony criminal penalties for counterfeiting or intentionally adulterating drugs as well as the monetary penalties are significantly higher and represent an attempt to deter those activities.

The new criminal penalty for counterfeiting drugs is up to 20 years in prison and up to a $1 million fine, and puts counterfeit drugs and the illegalities associated with the counterfeiting of sensitive products on a more even footing with the other counterfeiting laws in the US. Before FDASIA, McConagha commented, it was a much more serious crime in the US to counterfeit a handbag than it was to counterfeit a drug.

Prompted in part by the heparin crisis (see IPQ “Monthly Update” March 2012, p. 35), there is also a provision in FDASIA that institutes a 20-year felony penalty for the intentional adulteration of a product that results in serious injury or death. Under the law that preceded FDASIA, at most those who would perpetrate such crimes would be subject, at most, to a three-year felony penalty.

FDASIA increasing penalties is one of the prongs in FDA’s current anti-counterfeiting effort. In early October, the agency announced its “BeSafeRx” – a national campaign to raise awareness of the dangers of buying prescription medicines from fake online pharmacies. The campaign provides the resources to help consumers know more about online pharmacies, including: ● the risks of buying from ●how to identify those that are fake, and ● how to find one that is safe (link provided below).

Refuse Inspection, Suffer the Consequences

Another key provision of Title VII is a section providing FDA with the authority to disallow entry into the US of products manufactured at a facility that delays, denies, or limits an inspection or refuses the agency entry to inspect.

At the Xavier/FDA conference, Office of Manufacturing and Product Quality (OMPQ) Director Steven Lynn explained that under such circumstances drugs manufactured at the facility will be “rendered adulterated.” He added that if it
is a foreign facility, an import alert would probably be issued.

Within a year of FDASIA’s October 1 enactment, the agency is tasked with issuing guidance that defines what it means to delay, deny or limit an inspection.

**Adulterated or Misbranded Imported Drugs May be Destroyed**

FDASIA provides the authority to destroy imported drugs valued at $2,500 or less that are adulterated, misbranded, or counterfeited and have been refused admission into the US.

A due process provision allows for the destruction after notice to the owner and the opportunity to provide testimony opposing the destruction. The owner or consignee may be liable for the costs of storage and disposal.

Lynn pointed out that “in our international mail facilities, dietary supplements and other drugs being imported by unscrupulous individuals are a big problem. Now, instead of having to ship every single one of these back, we are going to have the right to destroy them.”

For the provision to take effect, FDA is required to issue regulations within two years of FDASIA’s implementation of that create the framework for providing for notice to a firm and an opportunity to appear before the agency. One aspect that will need to be clarified is how the value of the suspect shipment is arrived at.

**Trading Trade Secrets**

Section 710 of FDASIA provides FDA the ability to share trade secret information with foreign governments under specific circumstances and to receive such information, and exempts what is shared from becoming available to others through the Freedom of Information Act (FOIA).

Lynn explained that the inability to share the information “has been a big issue with our foreign counterparts over the past several years.” At issue is sharing inspection reports that are so heavily redacted as to render them useless.

The trade secret information may only be shared if certain provisions are met, including that: ● the information concerns the inspection of a facility ● the foreign government has the authority to otherwise obtain the information ● the shared information can only be used for civil regulatory purposes, and ● the information is protected from disclosure in the recipient country until the sponsor agrees in writing to disclosure, or in the event that the Secretary of Health and Human Services declares a public health emergency.

**Questions Raised on Track and Trace and Good Importer Practices**

Following their presentations, Trzeciak’s and McConagha addressed questions regarding the lack of a track-and-trace provision in FDASIA, how Good Importer Practices (GIPs) will be finalized and implemented, and the status of allowing accredited non-governmental third parties to conduct surrogate audits for FDA.

They explained that developing recommendations on a national track-and-trace system is a complex matter that had not been resolved in time to be included in FDASIA.

Work continues in Congress on moving forward with legislation in this area in a bipartisan and bicameral way, and the two staffers have participated in numerous discussions on the topic.

How long it will take to come to an agreement on the topic is uncertain, McConagha said, adding that the discussions to date have made progress and Congress recognizes the importance of trying to resolve the issues in a way that achieves the right balance between public health oversight and common sense regulation.

Regarding GIPs and how they will be implemented, Trzeciak noted that FDA already has guidance in this area, but it is not focused specifically on drugs.

She pointed out that the agency has already begun work on GIPs for drugs, and that it would need to work closely with US Customs and Border Protection – the agency charged in FDASIA with promulgating the regulations.

“We certainly want FDA to consult with those that have a history of importation,” Trzeciak pointed out. “We have heard from industry directly that they have engaged with FDA about this.” An important outcome of this engagement should be the Agency learning more about good importer practices from companies that have good systems in place. In turn, companies with good practices should be able to get their products into the country more easily.

McConagha pointed out that there is an effort to create a similar system in the Food Safety Modernization Act (FSMA), which passed a few years before FDASIA and is somewhat more mature in terms of implementation. What is learned from implementation for food products will likely be helpful to FDA and allow it to put a system in place more quickly.
Third Party Auditing Not in Final Bill

Discussion turned to the topic of FDA making use of foreign regulatory inspections, and whether there was a possibility of help from non-governmental third-party auditors.

A Senate bill had been proposed aimed at creating a third-party accreditation program, under which the agency could enlist private actors who would perform audits of foreign facilities that either FDA or its trusted allies had not been able to get to. These auditors could visit, for example, foreign firms desiring an inspection that fall into that category.

The idea was to create a system in which an accredited third party could go and perform the audit and submit those results to FDA, which would then have regulatory significance in terms of admissibility of the product.

However, the use of third party auditors for drug inspections turned out to be a controversial concept and did not make it into the final bill. McConagha suggested that the idea might be revisited after Congress takes a look at the success or lack of success FDA has with relying on inspection reports from other agencies.

An audience member queried McConagha and Trzeciak on why the provision was controversial, as an analogous system for foods exists under FSMA.

Trzeciak responded that there was “much discussion” regarding the provision and whether third parties would be able to conduct a drug inspection as thorough as those conducted by FDA.

Pointing to a poor history that third party auditors have had in other industries, she emphasized that it is important to ensure “that any third party system will have the same rigor that we see from an FDA inspection.”

Bar Raised for Excipients

During his presentation at the Xavier/FDA conference, compliance official Lynn explained that under FDASIA there will be new requirements regarding the listing of excipients in applications, but provided little detail. During the Q&A, a request for more detail was made.

Wearing his International Pharmaceutical Excipients Council (IPEC) hat, Colorcon Regulatory Affairs Director David Schonecker commented that he saw “a significant paradigm change that many people I talk to have not realized is buried in FDASIA,” regarding the requirement for excipients to be registered with FDA and for each excipient plant to have a unique facility identifier.

He pointed out that Section 703 of FDASIA requires that all sites used in the manufacture of an excipient must also be listed, which would include, for example, contract sites that grind or dry excipients manufactured at another plant.

“That level of transparency has never been really discussed between suppliers and customers in the past,” the Colorcon official stressed. “The new law is going to pretty much require that you have to list those sites in all your filings, and not only NDAs and ANDAs. The way our legal people have read it,” the provision covers covers all drugs, including over-the-counter products.

Noting that FDA will need to write regulations addressing how the requirements will be implemented, Schonecker asked Lynn for his thoughts on what those might look like, especially for OTCs that have a different filing system.

“There are many work groups across the centers working on various aspects of FDASIA,” Lynn commented. “In the coming months and years we will be working on the codification.”

Lynn predicted that the process would take into account industry input, adding that in his opinion “it would be silly not to.” The input process would likely be in the form of “either public meetings or some kind of Federal Register notice asking for comments.”

Schonecker added that it would appear there will need to be some sort of notification requirement if a firm changes its excipient supplier.

“There is a lot of discussion as to how that will take place,” he reported. “That is certainly going to be a huge paradigm shift. Most drug companies we talk to at IPEC don’t realize that is coming. They have not read that deeply into the law.”

Lynn commented that “it is going to be a lot of work for both our side and the industry side. But I think that hopefully we all can agree that it is best for public health to have this kind of transparency in the supply chain.”

Title X Addresses Drug Shortages

FDASIA Title X on drug shortages was included in the bill in response to a recent uptick in shortages – in particular, of generic injectable drugs – and provides FDA mechanisms to better manage and track them.

Specifically, the drug shortage provisions of Title X: ● expand drug supply disruption reporting requirements ● provide specific actions for FDA to take to mitigate or prevent shortages ● creates a mechanism for tracking data and sharing that information with key stakeholders ● creates a task force to analyze the causes of and devise a plan that addresses them, and ● provides for expedited inspections
and reviews of NDA and ANDA supplements that may help prevent or mitigate a shortage.

The increasing number of shortages of medically-necessary drugs, and of generic injectables in particular, received attention at public hearings held by Congress and FDA in September (see IPQ “Monthly Update - September 2011” p. 44).

In late December, FDA issued an Interim Final Rule (IFR) amending regulations relating to provisions of the Federal Food, Drug, and Cosmetic Act to require manufacturers who are the sole source of certain drug products to notify FDA at least six months before discontinuing product manufacturing (see IPQ “Updates in Brief” January 11, 2012).

In February, the issue of drug shortages along with a review of the final FDA proposals for the generic drug and biosimilar user fee acts (GDUFA/BsUFA) were the subject of a House Energy and Commerce Committee Subcommittee on Health hearing (see IPQ “Monthly Update - February 2012,” p. 2).

In late February, FDA announced additional steps to increase the supply of critically needed cancer drugs to help prevent drug shortages, including approval of a foreign substitute product and accelerated approval of a new domestic supplier. The agency also released a guidance clarifying agency expectations related to the mandatory and voluntary reporting of events that could result in shortages of prescription products (see IPQ “Monthly Update - March 2012” p. 11).

In April, the US House of Representatives produced a “discussion draft” of a bill directed at the drug shortage problem that was subsequently folded into FDASIA as Title X (see IPQ “Updates in Brief” April 11, 2012).

DOWNLOADS FROM THE STORY:
- FDASIA complete text
- FDA BeSafeRx website
- SAFE DOSES Act

FDASIA Annotated Table of Contents

Below is the table of contents for FDASIA with an explanation of what each section contains or changes.

I: Prescription Drug User Fee Amendments of 2012 (PDUFA V) – reauthorizes PDUFA; few changes from the 2007 reauthorization

II: Medical Device User Fee Amendments of 2012 (MDUFA III) – reauthorizes MDUFA; modifies fees and broadens the scope of establishments subject to registration fees.

III: Generic Drug User Fee Amendments of 2012 (GDUFA) – creates user fees for generic drugs

IV: Biosimilar User Fee Act of 2012 (BsUFA) – creates user fees for biosimilars

V: Pediatric Drugs and Devices – makes permanent the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA)

VI: Medical Device Regulatory Improvements – includes changes to the law for medical devices, improvements to the device recall program and harmonization efforts

VII: Drug Supply Chain – makes significant changes to enhance FDA’s inspection authority and help secure the drug supply chain

VIII: Generating Antibiotic Incentives Now – creates incentives to encourage the development of products for antibiotic-resistant infections

IX: Drug Approval and Patient Access – expands the scope of products that qualify for accelerated approval and creates a new “breakthrough therapy” program

X: Drug Shortages – addresses the current drug shortage crisis by enabling FDA to better manage and track shortages and potential shortages

XI: Other Provisions – reauthorizes certain provisions of the FDA Amendments Act (FDAAA) of 2007, provides for the regulation of medical gases, and includes other provisions, such as those on ● prescription drug abuse ● 180-day generic drug marketing exclusivity ● citizen petitions ● controlled substances, and ● nanotechnology.
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FDASIA’s Catch-All Title XI Includes Provisions on Medical Gases and Nanomaterials

A new system for the registration of medical gases and FDA participation in standard setting for nanotechnology particle-containing products are among the provisions in the catch-all Title XI of the Food and Drug Administration Safety and Innovation Act (FDASIA), that will further the Act’s impact on CMC and GMP regulatory processes.

Other of the 11 titles in FDASIA with significant CMC/GMP implications include: ● Titles I-IV on user fees user fees ● Title VII on the supply chain, and ● Title X on drug shortages (see the story on p. 4).

As is often the case in Congressional legislation, many of the provisions in Title XI represent a codification of significant initiatives already underway at the agency.

Under Subtitle B of Title 11, medical gases – which have been marketed in the past without agency involvement – will now need to be registered with FDA, with the exception of seven commonly-used gases that will be considered “designated.”

The designated gases are: ● oxygen ● nitrogen ● nitrous oxide ● helium ● carbon monoxide ● carbon dioxide, and ● medical air.

These gases will need to meet USP-NF or equivalent compendial requirements and labeling requirements, including a statement that they are for prescription use only as well as appropriate warnings, storage conditions and use instructions.

Medical gases that are not “designated” will need to file a request for certification within 180 days after enactment of the Subtitle B medical gas provision.

At a Great Lakes cGMP and Regulatory Science Forum at the University of Illinois Chicago in mid-September, Chicago District Drug Specialist Investigator Russ Riley commented that the medical gas requirements are “something new that affects my job an awful lot.”

He added that “very few parts of FDASIA are going to happen fast” and explained that the agency is considering now how to implement the various provisions through the promulgation of guidance and regulation.

In addition to the medical gas and nanotechnology provisions, Title XI also contains sections addressing: ● a requirement for electronic new drug application (NDA) submissions ● the need to define problems associated with internet pharmacies and new authorities required, and ● the advancement of regulatory science.

[Editor’s Note See IPQ’s July/August 2012 and September 2012 “Monthly Updates” for our recent coverage of GDUFA and BsUFA.]

Nanomaterials Need to be Understood

Under Title XI, FDASIA directs FDA to better understand nanomaterials and their implications when used in regulated products, and to participate in the development of consensus standards for these submicroscopic materials.

The agency is directed to “intensify and expand activities related to enhancing scientific knowledge regarding nanomaterials included or intended for inclusion” in FDA-regulated products, including investigation of the potential toxicity of the materials, their benefits, and the effects and interactions in biological systems.

To achieve these goals, the agency is urged to: ● assess scientific literature ● cooperate with other federal agencies to organize its information in databases ● participate in
collaborative efforts to understand, measure and detect nanomaterials ● analyze and disseminate information related to the interactions of the materials with biological systems ● build expertise on monitoring the production and presence of the materials in regulated products ● ensure ongoing training across FDA on new information learned, and ● participate in international and national consensus standards related to nanomaterials.

FDA has put in place a task force that is closely tracking the use of nanotechnology in drug products and exploring what further guidance and policy may be needed in the area (see IPQ May 2010 “Special Report”).

Submissions Must be Electronic

FDASIA directs FDA to issue guidance that will mandate electronic submissions of new drug and biologic license applications (NDAs and BLAs). Two years after the final guidance is issued, paper submissions will no longer be accepted.

As part of its guidance, the agency must include a timetable on implementation, electronic submission standards, and waiver criteria/exemptions to assist industry in making the transition.

This section is intended to complete the transition to electronic submissions that began in the early 1990’s.

At that time, industry began transitioning from strictly paper-based systems to computer aided new drug applications (CANDAs), using ad-hoc designs. In 1999, FDA issued an electronic NDA (eNDA) guidance, which outlined a formal electronic submission program.

The 1999 guidance was followed in 2002 by a guidance on electronic submission of abbreviated new drug applications (ANDAs) in electronic format, a 2003 guidance on submission of electronic common technical documents (eCTDs) modeled after guidelines produced by the international conference on harmonization (ICH), and a 2006 requirement that all CTDs were to be submitted in electronic format beginning in 2008. [Editor’s Note: A link to a 2009 presentation by CDER Office of Business Informatics Deputy Director Gary Gensinger on the evolution to electronic submissions is provided below.]

Internet Pharmacies Need Attention

Congress expressed its concern with Internet pharmacies in FDASIA by providing a section in Title XI that requires FDA to investigate online pharmacies and provide it with a report that describes the problems posed by the pharmacies that violate federal or state laws and the additional authorities the agency feels it needs to bring them under control.

Of particular interest are the methods that Internet websites use to sell prescription drugs in violation of the law, the harmful health effects that patients experience when consuming prescription drugs purchased through such a pharmacy, and the efforts by federal and state governments to prosecute the website owners or operators.

Congress also requested that FDA provide it with information regarding: ● the level of success that federal, state, and local governments have experienced in investigating and prosecuting such cases ● whether the law provides sufficient investigative authorities ● additional authorities that could assist in such investigations ● what laws, policies, and activities are needed that would educate consumers regarding sites that are legitimate and those that are not, and ● what activities the private sector is taking to address the prevalence of illegitimate pharmacy Internet websites.

Regulatory Should Promote Innovation

Congress also provided direction to FDA regarding the agency’s development of a strategy and implementation plan for advancing regulatory science in order to promote the public health and advance innovation in regulatory decision-making, consistent with provisions in the various user fee sections of FDASIA.

It directs the agency to: ● identify and provide a clear vision of the fundamental role of efficiency, consistency, predictability and science in its regulatory decision-making ● identify the regulatory science priorities directly related to fulfilling the mission of the agency with respect to allocation of resources, and ● identify regulatory and scientific gaps “that impede the timely development and review of, and regulatory certainty with respect to the approval, licensure, or clearance of medical products.”

Title XI also instructs the agency to identify “clear, measurable metrics” for gauging its progress in achieving the regulatory science goals, and requests that annual “performance reports” be submitted to Congress.
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New FDA Field Alert Report System Provides for Electronic Submission and Unique Identifiers

FDA is upgrading its field alert report (FAR) system to provide for secure electronic submission of the reports, simultaneous transmittal to the appropriate district office and the Center for Drug Evaluation and Research (CDER), and unique identifiers for each report.

The new system will be launched as a pilot with voluntary participation by industry, and is expected to begin by the end of the year. It is the product of an “improvement project” done jointly by CDER’s Office of Compliance (OC) and the Office of Regulatory Affairs (ORA).

FDA is moving to create a more efficient and effective field alert reporting process in the context of the concerns it has been voicing in 483s and follow-up enforcement actions with industry noncompliance with its FAR responsibilities (see IPQ “Monthly Update” May 2012, p. 16).

At a Global Outsourcing Conference (GOC) co-sponsored by Xavier University and FDA in late September in Cincinnati, Ohio, Office of Manufacturing and Product Quality (OMPQ) Director Steven Lynn explained that the project will be implemented in four phases over the next two years.

“Each phase will be rolled out incrementally in order to prevent disruption of business operations at ORA and CDER,” he explained. The gradual transition will allow firms “the opportunity to participate in standardization of the field alert reporting form, fields, and manufacturing data reported in the FARs.”

The four phases include transition from a PDF form that is now generally submitted to the agency as an email attachment or printed and mailed in hard copy, to a fully electronic form that will also use the Adobe PDF format including extensible markup language (XML). The existing form 3331 will be modified, but will retain the same form number.

The form will be completed online, and will include a “submit” button that provides for simultaneous submission of the field alert report to ORA and CDER.

“The old process,” Lynn noted, involved sending the form to the district office and the district forwarding it to headquarters. “Sometimes there was a time lag. Now it will go to both at the same time.”

Each FAR will contain a unique identifier, “which is going to be good for tracking reports in the future,” he emphasized.

In the current system, there is no unique number for each FAR.

**Standardization Benefits Industry and the Agency**

The new system is intended to decrease variability in the submission of FARs, allow integration of the reports with other electronic systems, and increase regulatory compliance – providing “a lot of benefits” that Lynn characterized as “exciting.”

It utilizes a “single submit mechanism” with a “single unified form” that will initially be sent via email, and eventually completed and submitted online. The new system will also enable organizations to enter data “efficiently” and “simplify data integration across the enterprise.”

Lynn explained that the new system reduces a pharma firm’s transaction time “significantly, without the need to print, cut and paste and copy paper files, which you have done in the past.” It will also allow firms to exchange files securely and electronically and can be integrated with electronic archive filing systems “so that there is no need to maintain both paper and electronic storage systems.”

The OMPQ director maintains that the new system will increase regulatory compliance by providing rapidly transmitted data that will “help us to follow up on defects quicker than we have in the past.”

He also pointed out that there are no software licenses or installation requirements.

The revised and automated form 3331 will be published “in the near future” along with directions for use. Also “forthcoming” are a Federal Register announcement, CDER points of contact to answer questions about the project, and a web page for the pilot.

“We will have an announcement for soliciting industry voluntary participation in the project,” Lynn pointed out. “And there will be a Q&A for industry on the project itself. Those will be coming in the next two or three months.”

**FARs in Focus for Customer Complaints**

The compliance problems FDA is seeing with field alert reporting and what it is looking for was provided by Atlanta district officials Penny McCarver and Bonita Chester at the University of Georgia/FDA GMP conference in March (see IPQ “Monthly Update” May 2012, p. 16).
During a Q&A session at the conference, McCarver stressed that firms should submit FARs for recurring technical defects discovered through the complaint process even when there is no evidence of the issues in site production records or retained samples.

She explained that a complaint – for example, about broken tablets – may be an indication of a problem occurring during product distribution.

“Even though you don’t see anything in your retained samples and you don’t find anything in the batch record, you still need to submit the field alert and you need to investigate,” she emphasized. “Just because it is not in your retained samples doesn’t mean that it didn’t happen out there in the field.”

Chester – a Level 3-certified member of the pharmaceutical inspectorate and resident-in-charge of the Atlanta District’s Greenville, South Carolina office – gave a presentation on the regulatory requirements for reporting field alerts and how the agency ensures compliance with those requirements. She provided examples of the kinds of problems that are reportable and how they should be reported.

The issue of consumer complaints that FDA maintains should have been submitted as FARS but were not has been prominent in recent regulatory actions involving both branded and generics companies.

Novartis received two significant 483s at its Lincoln, Nebraska solid oral dose OTC plant citing consumer complaints that the agency maintained should have been submitted as FARs. The 483 issued in January cited the lack of FAR submissions as a repeat observation from a July, 2011 inspection (see IPQ “Monthly Update” January 2012, p. 30).

The large generic injectable drug manufacturer American Pharmaceutical Partners (APP) received a warning letter earlier this year, also citing the lack of FARs submissions along with other complaint handling and failure investigation issues (see IPQ “Monthly Update” April 2012, p. 16).

A warning letter to a Baxter facility in Guayama pointed to a failure to report customer complaints for discoloration and particulate matter in its inhalation anesthetic Suprane. Numerous complaints beginning in 2004 led to an internal health hazard evaluation in by Baxter in 2009. However, the required FARs were not submitted, the warning letter maintains (see IPQ “Monthly Update” January 2012, p. 6).
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ICH Q10’s Role as Guidepost on Pharma Journey from “Blind Compliance” to Operational Excellence Affirmed at PDA/FDA Workshop

ICH Q10 is serving as an important guidepost on pharma’s journey from “blind compliance” to operational excellence, NSF-DBA Senior Partner Neil Wilkinson affirmed in his opening presentation at a PDA/FDA workshop in mid-September.

The workshop brought together senior quality and operations managers and key regulatory compliance officials to: ● take stock on where the pharmaceutical industry is on the quality systems implementation pathway ● examine the role that executive management plays in setting the pace of progress, and ● brainstorm on how to increase that pace moving forward.

In providing the context for the workshop discussions, Wilkinson drew on his extensive experience in pharma operations and quality management at AstraZeneca, his service as a representative of the European Federation of Pharmaceutical Industries and Associations (EFPIA) on the ICH Q10 Expert Working Group, and the insights he has gained as an industry consultant and trainer.

He assessed the past and current state of industry’s manufacturing and control performance and the regulatory environment it has been operating in. He then went on to explore the role that the evolving quality systems concepts enunciated in Q10 can play in addressing the shortcomings and strengthening quality cultures.

When in Rome…

Wilkinson gave voice to a theme that would be echoed throughout the workshop - that the key to industry’s advancement down the quality systems improvement pathway will be quality managers learning to speak in a language that company executives can understand and readily support.

The primary answer to the question of why companies need a modern effective pharmaceutical quality system (PQS) is that “it is good business practice,” Wilkinson said. However, quality people have not made this case clearly to their executive management.

“When the problem is that we always talk in ‘quality-speak’ - we talk in ‘technical-speak.’” Company execs, on the other hand, are usually lawyers or marketing people or accountants, “and those guys don’t actually understand what we are saying.”

Pointing out that the workshop is about the critical role executive management plays in empowering the PQS, Wilkinson stressed that “those of you in the quality arena all have a job to do, and that is helping senior leaders understand why it is imperative that we do this.”

The imperative reflects the more challenging environment in which pharma is operating and the cost it has naively been paying for quality.

“We cannot afford to keep throwing away money on 15% reject levels or high levels of complaints,” Wilkinson said.

In other industries, such as consumer goods, electronics or automobiles, the cost of quality “is the bread and butter of their organization. They have margins to meet…. They have to understand where every dime, every cent, is going. We have previously largely ignored that.”

Most pharma companies are not yet measuring the cost of quality. However, Wilkinson stressed, “that is how we convince the senior leaders that this is absolutely necessary. How much does it cost for a single complaint? How much does a recall cost? How much does an investigation cost? You then multiply that by the tens of thousands of investigations that some companies have and your senior leaders might wake up and take note. But we have not been very good at doing that.”

While pharma’s marketed products are generally safe and effective, “the cost of getting them to the market is obscenely high in our industry when you compare us with other industries…. We are quality dinosaurs compared to other industries and other industry sectors. We focus on compliance. We focus on box-ticking rather than understanding things and moving forward. The reality is if we had been in a truly competitive industry world – which many of our companies were not because we had such large margins that we could absorb all this - historically we would have become extinct.”

However, Wilkinson pointed out, “the world today is more challenging. Our margins are going down. Governments are not prepared to pay the prices that we want. There is much more generic competition.”

These pressures are leading more pharma companies to
recognize that “getting quality right actually will add tremendous value to the bottom line as well as protecting the patient.”

**Conception and Birth of Q10**

At the PDA/FDA workshop, NSF-DBA’s Wilkinson noted the following stepping stones on the pathway to ICH Q10:

- Reaction to ‘blind compliance’ mentality
- PricewaterhouseCoopers survey of pharma manufacturing - 2001
- FDA/PhRMA discussions on what are the problems
- FDA ‘cGMPs for the 21st Century Initiative/philosophy - 2002
- PhRMA /EFPIA groups seek to harmonise concepts via ICH
- ICH workshop, July 2003 – ICH quality vision agreed upon: Create ‘a single, harmonised global quality standard and interpretation based on good science and risk management principles’
- Evolved into the ICH trio: ICH Q8 Pharmaceutical Development / QbD ICH Q9 Quality Risk Management ICH Q10 Pharmaceutical Quality System

**“Operational Excellence” is the Password**

The situation presents a strong opportunity for a new kind of dialogue with senior management, the NSF-DBA partner stressed to the workshop attendees – a dialogue in which the emphasis shifts from GMP compliance to the more holistic concept of operational excellence.

Noting that pharma’s cost of quality is in the 20-30% range, Wilkinson proposed that “surely our CEOs and senior operating officers are interested in that figure.” They could do a lot more sales and marketing if that money were saved, he noted, “and we would have a better quality product, right first time, and a better supply chain that will guarantee the patients actually get the products.”

Underscoring the point that “GMPs have never given us a full quality system,” he emphasized that quality managers have the opportunity now to get clearance from the executive gatekeepers to cross this bridge, using “operational excellence” as the password.

OpEx and quality are viewed separately in many companies, and executives will often sign checks for the former and not for the latter. However, Wilkinson stressed, “we have to recognize that these go together.”

The importance of a quality system that links manufacturing and quality personnel together in pursuit of operational excellence was a theme that was echoed throughout the workshop presentations and discussions that followed Wilkinson’s presentation.

Among those providing different vantage points on this operations/quality connection at the workshop – and the role of management and the quality system and culture in forging it – were FDA compliance officials Steve Lynn and Rick Friedman and veteran industry quality leaders Gerry Migliaccio, who spearheaded Pfizer’s OpEx initiative over the past decade, Martin Van Trieste from Amgen, and Anders Vinther from Roche/Genentech.

**NSF-DBA’s NEIL WILKINSON ON THE PAST, PRESENT AND FUTURE OF PHARMA QUALITY SYSTEMS**

The opening presentation at the September PDA/FDA workshop on Q10 implementation was given by NSF-DBA Senior Partner Neil Wilkinson, who provided the context for the workshop discussions. Wilkinson analyzed the impact of the evolving quality system concepts on industry and the regulatory process, the past and current state of industry’s manufacturing and control performance, and where and how the shortcomings can be addressed moving forward. Borrowing from his extensive experience in pharma operations and quality management at AstraZeneca, his service as EFPIA representative on the ICH Q10 Expert Working Group, and the insights he has gained as an industry consultant and trainer, he made a compelling case for the need for industry to apply the Q10 principles and move from a quality-by-compliance to a quality-by-operational-excellence mindset.

I was given the challenge of talking about Q10, sharing experiences and how it came about, and why we need Q10. Basically I am going to condense about 11 years of history into 30 minutes.

Let me, first of all, ask you a question: How many of you in your organizations, in your roles, have a direct impact on quality? So who hasn’t got their hand up? The answer is that we all have direct roles in quality. I believe whatever role you are doing – in operations, engineering, planning, training, procurement, or whatever – you all have an impact on quality. I think that is the mindset of this conference that we are trying to move us to as we go forward.

We are going to talk specifically about Q10, but we are also going to talk more broadly about quality overall.
In the last five to seven years of my industry career, I had the privilege of being selected to be on the Expert Working Group working alongside Gerry [Migliaccio] and a number of others...in crafting the ICH Q10 document.

The first thing we should say is that Q10 came about predominately from the desire from industry. It was about us as an industry wanting to improve the situation that we were in. To do that, you have to work very closely with key regulators around the globe – predominately in the early days, it was with FDA – to change a culture often referred to as ‘blind compliance.’

This is about that journey. It is a journey – we are by no means anywhere near the finish line yet.... This is a marathon of a race. Will we make the finish line? It is up to you guys in this room and your colleagues. It remains to be seen.

Let's talk a little bit about these items – (see box on p. 17). The conception and birth of Q10 was painful. It was longer than an elephant's conception and gestation period. It took years. But behind it there was a lot of discussion and a lot of thinking that was not visible to a lot of people. I am going to try to take you in a nutshell through some of that as we go forward.

The question is, ‘why do we need a quality system in the first place? Haven’t we survived with GMPs through the 1970s and the 1980s?’ Some of us have survived – some of you haven’t. Some of you have fallen foul of some pretty tough enforcement activities. So we do need to think that if we get things right in the first place then we would avoid those and not have some rather large amounts of money to pay. We need a quality system because it is the right thing to do.

I will talk briefly about some of the key Q10 sections. I am not going to go through the fifteen or eighteen pages, but I will highlight some of the differences from the GMPs. And I will say at this point that we stole virtually everything that we have in Q10 from other industries, ISO standards, and good practices that we see around the world. So we weren’t particularly that clever. But we like to take praise when we can, and Gerry [Migliaccio] and I will accept a drink in the bar this evening from all of you. It was about stealing with pride and thinking what can we apply that other people do, that other industries do, that we were lousy at doing. Let's see...if we are still lousy at doing these as an industry.

And then briefly I will give you some of my views on where we are now. You can take them or leave them. But just think – in your chair, at your company – how do you feel about the journey at this point in time?

Conception and Birth of Q10

In the early 1990s, we had the generics scandal that began in the late 1980s. And FDA at the time, probably rightly, said ‘the trust is out the window’ – I think Commissioner McClellan used words to that very effect. The result was that everybody was treated in the same manner across the industry – at least any company that was supplying the US.

We threw our brains away. Basically if FDA came up and said, ‘dig a hole, Neil, six feet deep, jump in it and cover yourself up,' we would do it. It was the ‘blind compliance’ era. We were scared as an industry, full of fear – and FDA was ‘Fear, Depression and Anxiety’ in those days. It has changed magically since. But we lost our way as an industry.

Beginning about then were discussions between PhRMA – Gerry Migliaccio played a very key role in that – and some key FDAers, including Helen Winkel and others, who are still there behind that vision, saying ‘we have to work together to do this better.’ So the discussions began with PhRMA around 2001.

PricewaterhouseCoopers will share with you – you have probably read it – the outcomes of their survey. There were further surveys done on the state of the pharma industry, which were not pleasant reading.

Why were we so hopelessly inefficient and ineffective? Why were we not reaching the benchmarks that other industries were setting? Let’s be honest about it – we came up with all the excuses we could find to not move out of our comfort zone and change things.
The world has changed now. It is a very much more difficult environment for the pharma industry, for the economy overall, and we really do have to embrace these things to move forward rather than just thinking of the compliance factor.

These things progressed, and the FDA released something with what at the time I thought had a curious title: ‘GMPs for the 21st Century.’ It was much broader than that. It was a very interesting philosophy. It was actually issued on April Fool’s Day one year. And my colleague, who was with Lilly at the time in Indianapolis, rang me up and said, ‘hey, do you think this is a joke? Or do you think someone has actually posted this?’ Because the thinking behind it was so different than the previous years we had in terms of a compliance mentality. It was excellent thinking. It was all about ‘let’s move forward. Let’s start talking about risk-based approaches and science.’

I was involved in some of the PhRMA groups. I was also involved as the Chair of the EFPIA manufacturing group. We, sitting in Europe, actually liked this. We liked what the FDA was doing. ‘How do we get a slice of this cake?’

We partnered, essentially – with PhRMA and EFPIA joining together along with the JPMA from Japan coming in – and we took this thing one stage further. We actually decided that it would be nice if we could take this thinking globally, as the industry was by then moving rapidly much more globally, and maybe get it into ICH. And that was actually taken to the ICH workshop.

It was the only sunny day in Brussels in July 2003. Brussels is a grey place most of the year. It was wonderfully hot – 80° – and we were in the basement. I think it was the Radisson hotel. 40 or so people sweating away with no windows. And that was the conception. So I will let you think about what that was like.

After that, quite simply came these words – it took us two days essentially to come up with these words – ['create a single, harmonized global quality standard and interpretation based on good science and risk management principles.']. And if you look at them, that evolved eventually through the ICH process into Q8, Q9 and Q10. So remember that the three of them were born together and the intent is that they are used together – they are not independent guidances….

### The Modern Quality System

In our activities in training and educating people – which is what I do for a job today – I ask around the room, ‘why do we need a modern effective quality system?’

['It is good business practice'] is the answer that rarely comes up at the top of the list. That is the only answer. It is the primary answer. It should be simply that it is adding value to the business as well as the patient as well as delivering compliance from the regulatory perspective. It is incredible, however, how often people struggle to find the answer and it rarely appears at the top of the list.

Folks in quality sometimes have the difficulty of convincing senior leaders of this. The problem is that we always talk in ‘quality-speak.’ We talk in ‘technical-speak.’ We talk in gobbledygook. Senior leaders usually are lawyers or marketing people or sales people or accountants, and those guys don’t actually understand what we are saying. So part of my theme is to get this working. This workshop is about executive management and their impact. Those of you in the quality arena all have a job to do, and that is helping senior leaders understand why it is imperative that we do this.

If we look, the environment has changed. Our industry is facing more and more challenges. We cannot afford to keep throwing away money on 15% reject levels or high levels of complaints. The cost of quality is something that in other industries is the bread and butter of their organization. They have margins to meet. Possibly they are making consumer goods or are automotive manufacturers or suppliers to those industries. They have to understand where every dime, every cent, is going. We have previously largely ignored that.

There are very few companies in this room who, I can assure you, are measuring the cost of quality. There are some. There are some on the journey to doing that. That is how we convince the senior leaders that this is absolutely
necessary. How much does it cost for a single complaint? How much does a recall cost? How much does an investigation cost? You then multiply that by the tens of thousands of investigations that some companies have and your senior leaders might wake up and take note. But we have not been very good at doing that.

I should add that the products we are selling, by and large, are safe and efficacious. But the cost of getting them to the market is obscenely high in our industry when you compare us with other industries. People say, 'well, we are the pharma industry.' But isn't that our usual excuse for not doing something about it?

The world is changing. GMPs have never given us a full quality system. Actually, if you read the preamble to the FDA GMPs from way back in the 70s – 1978, I think – some of the stuff in there is what we are talking about today in Q10, Q8 and Q9. But somehow we missed the boat. We failed to interpret them in that manner. I would hasten to add that I think a lot of FDAers over the years have failed to interpret them in that manner. Go back and take a read of that. It was all about ISO 9000, which we all read in producing Q10. GMPs alone are not a quality system. They don't have various key elements that we now have in Q10. So they do need to be complemented.

**The State of Pharmaceutical Manufacturing 2001**

For those of you who remember 2001, PricewaterhouseCoopers came out with their report. It was hard reading guys, but it certainly resonated with me. This described where we were in 2001.

15% rejection rates – I was a production manager at the time. I used to plan in 20% extra batches of certain products because I knew that 20% or thereabouts would fail. I had no idea why. Some campaigns did, some didn’t. So how near to the edge of the process capability I was I didn’t know, because we weren’t measuring process capability. That was something our suppliers did. We were the pharma industry – we didn’t need to do that. I think we are learning now.

Scrap and rework was at 5-10% and we tolerated it. I went to Munich once and I took a tour of the BMW three series factory there. I was talking to someone there and I told him I was in health care. He said, ‘your quality must be absolutely fantastic.’ I said, ‘look at your line for the beautiful three series sedans – beautiful cars coming down the line. Let’s count the cars – one, two, three, four, five, six, seven, eight. Ok, throw that one away.’ He looked at me and smiled. He said, ‘I do not understand, Neil, what are you saying?’ I told him we throw away about one-eighth of our batches. He laughed and said, ‘no, you are joking.’ I said that I was not. So we have a long way to go.

The cost of quality, if we did measure it – as some companies are doing now – would be 20-30%. That is a lot. Surely our CEOs and senior operating officers are interested in that figure. They are certainly interested in sales and marketing budgets – they always get what they want. Just think how much more sales and marketing they could do if we actually saved them that amount. And we would have a better quality product, right first time, and a better supply chain that will guarantee the patients actually get the products.

You have seen the quote from Commissioner Mark McClellan from 2001. ['You need to improve.... Other high-tech industries have achieved enormous product gains in manufacturing in the last 25 years. We should expect nothing less from the pharmaceutical industry.'] Let’s get moving forward.

There was then recognition that we are not as good as we should be. Why is that? What is the problem? How can we move this forward? While we were strongly defending that we did not have unsafe products on the market, it was very clear that we were neither at the leading edge of technologies or efficiency, either. So we began to realize that we have to do something about this.

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**Woodcock’s 2004 Report on the State of Pharmaceutical Manufacturing**

The following are key points in Janet Woodcock’s 2004 report to the FDA Science Board on the state of pharmaceutical manufacturing:

- Pharmaceutical manufacturing is not fully utilizing modern manufacturing technologies and quality management approaches
- Manufacturing expenses exceed R&D investment
- Perceived regulatory barrier to improvement
Then you take a look at that headline [Wall Street Journal 2003: ‘The pharmaceutical industry has a little secret: Even as it invents new drugs, its manufacturing techniques lag far behind those of potato chip and laundry soap makers.’] And you try to explain to your children as you are going to work: ‘I am a senior manufacturing manager or I am a senior quality head in pharmaceuticals – wonderful. Potato chip manufacturers and laundry soap makers have better systems in manufacturing, better measures, better feedback, better understanding of process capability, better quality than we do.’ It is still the case in many areas. It is embarrassing. Many of us were horrified when we read that.

FDA started looking at this. They started asking us, ‘why?’ With the help of PricewaterhouseCoopers and PhRMA and others, I have to say there were some very open and cordial discussions. There was recognition that pharma wasn’t doing it very well. But also there were some perceived barriers there as to why we weren’t doing it well, including the difficulties of making change.

The Desired State

Some of those barriers were in our own minds as industry….We did not talk to the FDA. We did not ask them. We just said, ‘stop that change, we can’t do it, we will stay as we are’ and reject the next batch.

That culture is changing. These were words that Janet [Woodcock], Helen [Winkle], Moheb [Nasr], Ajaz [Hussain] and others came up with in FDA (see box). That’s pretty good, isn’t it? And we are still on that journey. That was published in 2004….

But FDA stole these as well. It wasn’t the geniuses in FDA – this is Deming. When I was born, Deming was around doing his good work. And I wasn’t born yesterday, as you can tell. I have a few gray hairs….

So you are thinking that if all this is available, why aren’t we doing it? How can we help change things? Ultimately Q10 is one of the pieces of the jigsaw puzzle that came about as a result of it.

We do see some companies now trying to do quality by design for some new products and processes, measuring them and actually having real-time release and types of control strategies that are far more effective than the dreadful end-product testing that we relied on for years and years.

FDA’s 2004 View of the “Desired State”

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight.”

- Manufacturers have extensive product and process knowledge
- Manufacturers strive for continual improvement
- No manufacturing supplements needed
- FDA role is verification and subsequent auditing of QS
- Adjust level of regulatory scrutiny commensurate with patient risk
- Use limited resources to focus on more important issues

The Current State of Pharma Manufacturing

We had a reminder in 2005. We were getting a little bit cocky then, thinking that we were not that bad. Then IBM published a report that is still available – I have a copy if anybody wants one. It was titled ‘The Metamorphosis of Manufacturing.’ Same stuff again as PricewaterhouseCoopers. In four years we had not really moved forward.

It does tell a lot of things about our industry. And we are actually better than these now. Most companies now have started or have programs around measuring and understanding their processes and process capability. Actually if you do that you have less work to do in validation to maintain a state of control, because you know instantly whether a batch is going out of control.

2.5 sigma processes – the electronics industry and others are at 10-12 sigma now, way ahead of where we are. These are the benefits that are available year on year to our industry if we could actually make it happen. That would be nice to have. Wouldn’t everybody in this room like a slice of that pie?
So where are we currently? That's the way we evolved, and that is where we are now. We are into this implementation journey that began four years ago when Q10 was published in the different regions. So we have had four years to think about it. Where are we now in implementation?

We are quality dinosaurs compared to other industries and other industry sectors. We focus on compliance. We focus on box-ticking rather than understanding things and moving forward. The reality is if we had been in a truly competitive industry world – which many of our companies were not because we had such large margins that we could absorb all this – historically we would have become extinct.

I think the world today is more challenging. Our margins are going down. Governments are not prepared to pay the prices that we want. There is much more generic competition. More and more companies now are recognizing that getting quality right actually will add tremendous value to the bottom line as well as protecting the patient.

Why don't we change? You tell me. So many companies that I know from working with them are well on the road to a change program. Some of you are still throwing the dice waiting to be told that this is the thing to do. It is your choice as companies.

Here are some of the reasons from my view why we don’t move forward as quickly as we could. I am not going to dwell on them.... But there are some key things here. Quality is not recognized. We have allowed this legal requirement – which isn’t going to go away – for independent quality units to drive the wrong behaviors in our companies. It is ‘us’ and ‘them.’

Quality professionals should be adding value – making the right decisions based on education and knowledge that adds value to the business. It shouldn’t stop the business. Everybody should have a quality mindset, not just the Q unit. And though we all say this in our companies, how does it actually feel in your company? It will vary across this room, having looked at the attendees list, as to whether it is truly part of management or it is just something that is tacitly thrown over to the quality group to sort out.

The Economics of Quality

We get used to rejects and defects, and that is tolerated, it is routine. If we are going to make progress, people need to understand how much this actually costs to convince senior leaders to invest the money for us to improve.

It isn’t rocket science. There has been an ISO cost of quality model – it is only three or four pages long – out there for years. All we have to do it interpret it. You don’t have to do it all, but do parts of it – the 80/20 rule – and you will start identifying where you are wasting most of your money and then you can target your improvement activities. It is made...
up of these boxes and not that difficult in theory. In practice it is more difficult, but it is the right mindset.

You have to get financial people on board. How often do you have financial people in your quality review meetings? How often do you have procurement people who tell you that they will save you lots of money by sourcing from China? Are they really measuring the total cost of ownership and the total cost of quality or just the price per kilo? Then they leave and quality has to pick up the mess later.

There is a lot in this that we can learn. And Q10 does not specifically say that you need the cost of quality. But it implies that you have to have things that you are measuring so that you can then drive improvement. It is not specifically mentioned, but it was in our thinking.

You need a balance between the preventive approach and the reactive approach. We have glorified in the reactive approach and fire fighting. We love it, don’t we? Friday afternoons, public holidays – ‘yes, it’s a recall!’ Or ‘yes, it is a potential sterility failure!’ We start doing the investigations and spend the weekend there rather than with the kids and the family. But seriously, we have to move to a much more preventive approach.

ICH Q10 Key Elements

So Q10 came along with all that thinking. There were probably six or seven years of thinking behind us when we built all these things in. We came up with three simple objectives for Q10:

● Achieve product realization – that is not just about the initial design and development and then throwing it over the wall to manufacturing. It is about the lifecycle. It is about learning.

● It is about constantly monitoring, measuring, understanding and keeping on top of the products and processes to keep them in a state of control, which is the next phase. So if you know what your issue is, you can measure and monitor it in real time and be able to react instantly to it rather than waiting three weeks for the lab to tell you the whole campaign has failed.

● Absolutely key here – something that has never before appeared in pharmaceutical documents, although it is an expectation of the GMPs and the regulators – [is continual improvement]. We use all this then to decide as a company which areas we now need to improve.

Obviously patient safety-critical areas you would do first. There are other areas you might say that you can tolerate for a while, because you can’t do everything at once. But the concept has to be there that management is involved in the process.

Q10 has five simple parts to it. And the absolutely critical one that this conference is not exclusively but largely based on is the commitment of management – developing the culture in the organization. Culture is a word that started creeping into these meetings. I think it has gotten more and more importance, because the top level culture in the company – and that is not just words and fancy signs in the entrance lobbies – needs to be really built in at all levels though the organization. If you haven’t got that, you are not going to be able to drive forward quality and improvement. There are many companies in this room that are still striving and thinking ‘where do we fit’ in terms of
quality approaches.

So what do we have in Q10 that we didn't have before? That is what we have in Q10 (see box).

GMPs are still there. We couldn't change the law. GMPs are still the law in each of the regions. So the GMPs have a little bit about management, but it is not that explicit. The European GMPs have it, but it is very limited. FDA has expectations, but it wasn't written into the CFR.

We think about ISO 9000, which we stole from dramatically. There are some elements in there around risk and knowledge management and the lifecycle. ISO is much stronger in terms of continual improvement and much stronger in terms of management responsibilities. ISO is general to quality systems overall, it is not just pharmaceuticals and good manufacturing practice.

We still have the FDA quality systems guide. That evolved at the same time as ICH Q10. The two were being developed at the same time. Some common people worked on both. So it is not surprising that there is a lot of commonality. That includes the whole raft of these areas. So it much more than just the GMPs we preached about.

I asked at a previous PDA/FDA meeting [on ICH Q10 in October, 2011] (see IPQ “Monthly Update” November 2011, p. 39) either last year or the year before, ‘how many of your CEOs actually understand quality as opposed to compliance?’ I won’t embarrass you guys – I am running out of time. But the answers were around one-third when we asked a US audience. It was slightly more in Europe, but not many. So that means that at least half of them don’t actually understand the importance of quality, which probably means somewhere there is [someone] that can actually articulate it in a manner that they can understand. Or maybe they are just dice rollers – the guys who will roll the dice until they are called out by the regulators.

Absolutely critical are not just the internal activities, it is also all the outsourced activities. They are a management responsibility as well.

When we wrote Q10, the Heparin crisis was actually happening, so there was understandably a major focus on outsourcing at the time, which is why you find in Q10 a lot more detail on outsourcing than you find in some of the other sections. It is critically important.…

We have to make sure that we are continually improving in all these areas, and in Q10 there are sections that address that. We were completely missing doing that before. We were doing annual product reviews, but why were we doing them? Mostly just to tick the box and say, ‘hey, FDA inspector, we have done the annual product review,’ even though it may be three years late. We are much more moving toward doing it promptly in real time so that the information and knowledge is used for the company to improve, not just to satisfy a regulatory requirement.

So there are a lot of differences. I used to go to companies and say, ‘show me your quality system,’ and they would give me an index of their SOPs. I said, ‘no, that is not the quality system – that is 4,200 SOPs.’ In the first place, that
is too many. Secondly it isn’t a quality system. It doesn’t tell me how they all link together. Which are the lifecycle bits? Which cross boundaries between development and medical and operations? It is well beyond that.

Q10 actually has some new expectations, but also beeps up some of the existing GMP areas. Most importantly, I might argue, it introduces concepts that have been routine in other industries for many years. And we are struggling with some of that. We also have to bring in people from outside the industry to make it work.

**Implementation Progress**

Where are we now in implementation? I see a wide range of variability. It is a journey. There isn’t a requirement anywhere yet that says ‘you will be fully compliant by March 3, 2013.’

The other thing to say is that **one size does not fit all**. Q10 is written to be deliberately flexible, recognizing that we have: fully integrated R&D companies; outsourcing; virtual companies; small companies; large companies; generics; CMOs, etc. It is written to be interpreted by each of those so that they can then develop their own quality system.

I think there is a perception that there has been a slow uptake by industry. Whether that is true, I don’t know…. I think there is still some uncertainty of the regulatory status of Q10. It is an expectation, guys, it is a CGMP. So therefore it is soft law. It may not be written in the agency laws, but CGMPs are an expectation of the agency in the United States. In Europe it is being published. Of course, Europe couldn’t make its mind up, so it is a guidance, but also some EU GMP chapters are being added to and beefed up with words straight from Q10. So if you think that it is a weak little guidance that will go away, I don’t think so.

Somebody in this room, I don’t mean to embarrass them, but a very senior person said these words: ‘Why wouldn’t a firm implement Q10? It makes complete business sense.’ It has nothing to do with regulators. It has nothing to do with flexibility. It makes absolute sense to do it. So why do we as an industry struggle with something that is apparently common sense?

What are some of the implementation strategies that have been seen?

- Absolutely critical [is] top level and cross-functional business unit support to get an active quality system across a company – particularly a larger company.
- It certainly cannot be seen as a quality initiative or project. It is a culture change. It has to be driven by the top. If quality is leading it alone, it will not succeed, or it will be very difficult for it to succeed.
- You need a business case. When I began to put the concepts of Q10 into AstraZeneca, my old company, even though I was on the Expert Working Group, they gave me a hard time. They said, ‘why should we do it, Neil? You have just been off traveling the world for three years. Why should we do this?’ And we had to produce evidence that financially it was the right thing to do.
- Start small. It is a big elephant, so it is perfectly acceptable to take bits of it and start working to introduce those bits into your existing quality management system.
- Ultimately, don’t wait until you get a letter from Steve [Lynn] or Rick [Friedman] saying that you have to do it. It is much more painful and much more expensive to have to do it that way than doing it yourself.

We won’t see specific references to ICH Q10 in 483s, because it is not the law, and the 483s refer back to the CFR. But we are seeing references to the sorts of comments, which are essentially where the FDA is saying that you are not following Q10 principles. Inspectors will be looking at these areas [corporate and management oversight, adequacy of quality unit, deviation and complaint/CAPA effectiveness investigations, and out of control processes].

Don’t think that it is just a guidance. It is an expectation.

These are sobering thoughts. Let’s depress everybody. Just read those words – you may have read them before. I showed you Janet Woodcock’s thoughts in 2001. These are Janet’s recent comments from a public meeting (see box on p. 26).
It seems to tell me that maybe FDA, who has really tried to drive this forward with industry, have a few concerns that we are not doing all we should be doing as an industry. That is pretty hard reading. She did not say those words without discussions with people in this room and other people.

And the reality of all that really is that this will not change if we don’t, as an industry, take advantage of the opportunity of what we have put into Q10, which builds on many years of discussions, then we deserve what we get. It is an opportunity. Those that take it, I am convinced, will benefit. But we have to do it as an initiative that is a business-level initiative. It has to on-board senior leaders – and not just them putting their face on a nice glossy newsletter, but actually believing in it.

When you go to a senior leadership board meeting, you should see the quality guy next to the CEO. Whenever I have been to those meetings, it is the sales guy or the accountant or the sales and marketing guy. There is something that doesn’t quite go in our industry, and we have all got to work to change to make this happen. It is not easy. But that is where we have got to go.

So I think that we – and that is all of you in this room as well as me and others – have got to try and take this opportunity.

And by the way, there are some great talks about operational excellence this next day-and-a-half. Operational excellence and quality fit together in the same bucket. Why do we try and separate them in some companies? Why do senior leaders always sign the check because operational excellence is the only logo on the proposal and never sign it as quality? That is the mindset we have to work with. You are laughing because you have been there as well as me – some of you are laughing. But we have to recognize that these go together. That is not stepping over the line of the independent quality unit. That still should exist. But we still have to get the operational excellence bit alongside quality.

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**Recent Views from Janet Woodcock**

*The following are some of the observations on the current state of pharmaceutical manufacturing made by CDER Director Janet Woodcock at the ISPE/FDA CGMP conference in June:*

“Quality management in the pharmaceutical industry still lags significantly behind other manufacturing sectors.”

“Most of the recent high profile drug recalls, drug shortages, etc, can be traced to the complete failure of the firm’s quality management system.”

These recall and shortage problems have led to “lost revenue, damaged reputation of the firms, lost jobs, and in some cases, the possible loss of a company” and “were the consequences of allowing the quality system to fail to the point where all these other problems occur out in the public eye.”

“Clearly in many of these cases…the management is not paying attention to what these problems are.”

“All of these failures suggest a QMS that is insufficiently empowered or resourced to adequately carry out its essential functions.”

The recent spate of manufacturing problems “will need to be a focus for the FDA in evaluating additional steps it might take in response.”

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International Dialogue Should Focus on Harmonizing Control Strategy Filings and CMC Change Requirements, Moheb Nasr’s Industry Experience Confirms

Moheb Nasr’s recent experience as a leader of global CMC strategy for GlaxoSmithKline (GSK) has reinforced his conviction that the international quality regulatory dialogue should focus on clarifying and harmonizing the filing expectations for the control strategy as a lynchpin in the advancement of the quality-by-design/continuous improvement paradigm.

At the Drug Information Association (DIA) annual meeting in late June in Philadelphia, the former director of FDA’s Office of New Drug Quality Assessment (ONDQA) reaffirmed the case he made while at the agency that agreement around the control strategy expectations could provide a risk- and science-based platform for a unified global application and post-approval change regulatory approach (see IPQ “Monthly Update” June 2011, p. 20).

Nasr joined Acting ONDQA Director Christine Moore and EMA International and European Cooperation Sector Head Emer Cooke in addressing a session of the DIA meeting focused on manufacturing changes.

Drawing on his experience with GSK, with CMC policy setting at FDA and with the development and implementation of the ICH Q8-10 guidelines, Nasr explained the challenges industry and regulators face in advancing the new paradigm and where the pathway forward may lie (see box below).

What is needed, Nasr maintained, is for industry to become more transparent about its QbD knowledge base in applications so that the agency has the confidence to allow the self-regulation of manufacturing changes and the application review process can serve as a springboard rather than a roadblock for continuous improvement.

The current system, he stressed, “is not only challenging for industry but also for regulators. It is very complex, costly and resource-intensive.”

What bothers him most as a scientist is that “it discourages transparency in the regulatory filing – there is a lot of discussion in industry about how much or how little information needs to be in a regulatory filing. It hampers innovation and continuous improvement. I will also argue that it is responsible, at some level, for drug shortages and checklist approaches.”

The key lies in clarifying to industry what information provided in the application is considered a regulatory commitment, Nasr maintained. “Without that, we will never have regulatory transparency. There will always be a desire to put in as little information as possible. Is this the right approach? I hope not.”

“What is needed now more than ever before,” he affirmed, “is bold leadership to meet the 21st century expectations – not to make minor changes on 25-year-old guidances.”

Focus on Control Strategy

Nasr suggested that the issue of what information to file could be solved, in part, by focusing attention in the application on the firm’s control strategy.

The control strategy, he noted, “is the key regulatory part of the filing to assure quality, safety and efficacy, and should serve as the primary regulatory commitment.”

Additional information “needs to be there for transparency and to share the science,” Nasr said, “but it should be there as supportive information intended to facilitate the review, assure fitness for use, and robustness of the control strategy.”

Focusing on the control strategy could also provide a path toward greater regulatory flexibility in making manufacturing changes and help foster innovation and continuous improvement.

Demonstrated process and product understanding and a robust control strategy “could lead to significant reduction in post-approval manufacturing supplements,” Nasr maintained. “That means that the more you know, the more the agency trusts the manufacturer to manage many of the changes without regulatory approval.”

He asserted the need for pharma companies to focus more on innovation and new technologies and commented on how the current system hampers those activities. “This may get me in trouble, but in comparison with other industries we are considered in the dark ages with respect to zero defects and overall efficiency. This is not a good way for pharma companies to be in the 21st century.”

NASR Sounds Call For Global Initiative

With Nasr’s encouragement, CMC review policy makers in the US and Europe have been placing more emphasis on the control strategy as the nexus for the advancing pharmaceutical QbD regulatory paradigm (see IPQ “Monthly Update” June 2011, p. 20).

That emphasis is findings its way into the renovation...
underway of FDA’s generic drug review process. The assessment by the Office of Generic Drugs (OGD) of its growing body of experience with QbD-oriented applications is revealing the need for sponsors to convey a more in-depth and coherent control strategy to reviewers in applications if the benefits of the new paradigm are to be fully realized (see IPQ “Monthly Update” September 2012, p. 11).

The application commitment and manufacturing change concerns need “urgent” attention across the global regulatory landscape, Nasr stressed – potentially in the form of additional harmonized guidance.

“There is an interest now in what some people consider one global submission – that one submission will be sufficient for the entire world if it meets some rigorous and robust internationally-recognized quality standards.” To move in that direction, he said, the control strategy and change management are the “two big ticket items” requiring attention.

Noting the experience gained with the ICH guidelines and global cooperation, Nasr suggested that an industry/regulator forum be held to address the “urgent” issues around the optimum application format for the control strategy and how to create a science- and risk-based approach to the criteria for change management.

“We need open, frank and candid discussion about where we are and where we need to go,” he said, and potentially two “major” harmonized guidelines in these areas.

Modernize Change Management Before Harmonizing

In her presentation at the DIA session, ONDQA’s Moore also advocated the need for harmonization around post-approval change management and suggested a similar view of what that should look like.

Moore had the opportunity to serve directly under Nasr at FDA and help him advance the Q8-10 quality regulatory paradigm. She became acting director when Nasr left the agency in the Fall of 2011.

Like Nasr, Moore advocated the desirability of changing the regulatory approach to change management rather than tinkering with the status quo.

“One of the things that I realized when putting this presentation together,” she commented, “is that I don’t think we want to harmonize what we currently do for post-approval change management. What we want to do is modernize our post-approval change management first, and then work at harmonization either later or simultaneously.”

In her presentation, Moore shared ONDQA’s experience with change protocols, current CMC guidances that she feels need updating, and steps that the Center for Drug Evaluation and Research (CDER) is taking to modernize its CMC processes.

Noting that her office has seen “many” change protocols recently in QbD-containing applications covering a “wide variety of topics,” she explained that a number of them are for change of manufacturing sites or alternative manufacturing processes or analytical methods. Others are for expansion of design space and implementation of real-time release testing (RTRT).

Moore noted that she has seen changes that contain a “wider scope” than what is in the current draft of the comparability protocol guidance. “We are looking to update that guidance in the near future,” she said. “It will come out as another draft for comment.”

Related deficiencies reviewers are seeing include a lack of required information or reporting category in the change protocol, and information that is put in applications that should instead be submitted in a change protocol.

“Sometimes they don’t tell us what studies they are going to perform to evaluate the effect of the change or how they are going to accept the change,” Moore commented.

She pointed out that claims for regulatory flexibility do not belong in the body of the application. “They should be specified as a protocol, because you are talking about making changes to the application and changing the reporting category.” She explained that such requests will be considered and could be discussed in the context of a Phase II or pre-NDA meeting.

Change Guidances Need Updating

Moore commented that many of ONDQA’s related guidances are “old” and in need of updating to reflect QbD thinking.

As an example, she pointed to the 1995 scale-up and post-approval changes (SUPAC) guidance, which uses a risk-based approach, but categorizes “everything within the same dosage form using the same risks. This is not always a good assumption for all products.”

Moore also noted that although the agency has established “this great science and risk-based structure for what you put in the initial submission, we don’t have clear rules or clear guidance on how to use that post-approval…. We have evolved the science- and risk-based approaches under QbD,
but we have not provided additional flexibility beyond design space, for, say, RTRT and related those to post-approval changes.” However, that is where she sees “the future going.”

The ONDQA leader provided insight on how CDER is dealing with older guidances and moving toward international harmonization.

She explained that CDER has “reformed” the Council on Pharmaceutical Quality (CPQ), which is now tasked with, among other things, “shaping the future of CMC quality, including change management and what is appropriate for supplements.”

The center will be asking for suggestions “soon” on how to modernize its change management approach. “You will likely see this in an unexpected place,” she commented – in a rework of the draft SUPAC manufacturing equipment addendums. “When the rework of that guidance comes out, we plan to open a docket for public comment.”

Regarding potential areas for harmonization, Moore explained that most requirements, with the exception of how to file changes, “should be independent of regional requirements. It is a science- and risk-based approach regardless of what language you are in. Now granted, not everyone always has the same approach about science – that won’t necessarily be the same – but it is a place to start.”

**Similarities Provide Harmonization Opportunities**

In the same session, EMA’s Cooke offered an EMA perspective on the opportunities for harmonization around post-approval changes.

She pointed to the better alignment that exists now between the US and EU in areas such as quality management expectations, risk classification and annual reportable changes.

Prior to the new regulations in Europe, there was no provision for annual reportable changes, Cooke pointed out, calling the new regs “a move in the right direction.” She added that “in both the EU and the US, we use the ICH foundations for the dossier content and also the approaches to quality by design, risk management and quality systems.”

In addition, the use of the common technical document (CTD) in both regions ensures that the same information goes into the same part of the dossier regardless of region. “That applies in the post-approval change pathway as well,” she stressed.

**However, she noted, obstacles remain on the US/EU harmonization pathway.**

For example, the granularity of the approaches differs. “In Europe, we have a very granular approach to the levels of the types of changes and provide very specific details and require specific documentation.” The regulatory procedures are also “very different. Despite the fact that we are still moving closer together, it is still difficult for companies to manage changes in an international context.”

The EMA official pointed out that the new EU rules provide “more scope for harmonization” and that fewer changes will require prior approval. Also they allow for the possibility of change management protocols and annual reports.

She noted that the joint US/EU QbD review pilot (see IPQ “Monthly Update” February 2011, p. 42), which focuses on complex applications challenging to both regions, is serving as another link in the harmonization chain.

The addition in the EU of a provision for a post-approval change management protocol also provides an avenue to move forward in “managing timing and procedures internationally.”

EU’s new post-approval change management protocol is “very similar” to the FDA protocol, Cooke explained. “It basically asks to describe up front what you intend to do, how you would like to implement it, and how what you intend to do would be verified at a later stage.”

**GSK’s MOHEB NASR ON POST-APPROVAL CHANGE PATHWAY CHALLENGES AND OPPORTUNITIES**

At the June DIA annual meeting, GSK Global CMC Strategy VP Moheb Nasr reaffirmed the case he made while ONDQA director and ICH Q 8-10 IWG member that agreement around the control strategy filing expectations could provide a risk- and science-based platform for a unified global application and post-approval change regulatory approach. He addressed: • regulatory expectations and challenges • lifecycle management • limited regulatory opportunities • GSK’s experiences • challenges and opportunities • a way forward, and • possible next steps.

I will go over some regulatory expectations, share with you some of the challenges with lifecycle management, discuss lessons learned from recent regulatory initiatives – some worked well and some did not realize the benefits that we all
thought they should realize – and learning from this how we can move forward. There is no reason to reinvent the wheel, but I think it is important for us to learn from the previous lessons before moving forward.

With that being said, if I were sitting in your place late in the afternoon, I would say, 'change management again? That is a topic that has been discussed for years and years.' Another question I would raise if I were setting in your place is, 'whatever happened to the promise of regulatory relief?'

There have been several regulatory initiatives, starting with the GMPs for the 21st century, process analytical technology, quality by design, ICH Q8, Q9, Q10 and Q11, and the new variations regulation in the EU. And each one of these initiatives brought in a promise of simplifying change management.

I think a key question for us today…is how we can effectively have a paradigm shift to simplify expectations and compliance?

**Regulatory Expectations and Challenges**

I think you already heard about the regulatory expectation that the manufacturer is responsible for quality and assurance that changes do not have a negative impact on quality, safety and efficacy. The processes vary from simple notification to waiting for approval prior to implementing the change.

I think it is important for everyone here to realize that quality by design did not change the regulations. However, there are new strategies that can be put in place to meet the existing regulations.

I am going to focus today on some of the current challenges and offer you a proposal to move forward.

I think the current system is not only challenging for industry but also for regulators. It is very complex, costly and resource-intensive. I think what bothers me the most as a scientist is that it discourages transparency in the regulatory filing. There is a lot of discussion in industry about how much or how little information needs to be in a regulatory filing. It hampers innovation and continuous improvement. I will also argue that it is responsible, at some level, for drug shortages and checklist approaches….

**Lifecycle Management**

CMC lifecycle management is becoming increasingly critical. There are a lot of drivers that a manufacturer will have to address and to make changes, including: ● manufacturing efficiency ● security of supply ● response to regulatory developments ● advances in technology ● increase and product and process knowledge, and ● commitment to making continual improvements.

There are several types of lifecycle changes. If you change analytical methods, in some regions you have to submit that change and wait for approval. Also quality-by-design related changes, whether extension of design space or updating the control strategy. Sourcing and manufacturing site changes and process improvements are also the basis for changes in manufacturing processes.

I would like to focus today on this: In the 21st century we should focus more on opportunities to introduce innovation and new technologies. This may get me in trouble, but in comparison with other industries we are considered in the dark ages with respect to zero defects and overall efficiency. This is not a good way for pharma companies to be in the 21st century.

**Limited Regulatory Opportunities**

We have had a lot of different regulatory initiatives in recent times – for example, ICH Q8. Being in the working group that developed the guideline, I recall vividly the very heated discussion that we had about putting specific language in the guideline that the ‘degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided.’ Added to that were opportunities to facilitate flexible regulatory approaches.
I would argue that many of the things we have made progress on. But in the end, very little progress has been made on reduction of post-approval submissions.

There was also a recent guidance issued by FDA in June 2010, about downgrading some CBE-30 and CBE-0 submissions to annual reportable. Many were essentially administrative changes. I would also argue that the outcome of this guidance is not what was expected earlier, and I would urge FDA to assess its value and implementation progress, if any.

EU has made tremendous changes in its variation regulations. As a matter of fact looking at Emer Cooke in this room, and I see Joe Famulare in the back, I recall a meeting where the three of us were in Brussels thinking about the development of ICH Q10. The EU made a commitment at that meeting to revise the variations regulation. And it did. And it did a great job. I see a lot of opportunities here that I would like to highlight.

One is that continuous improvement in manufacturing should be supported by providing further flexibility to manufacturers who have taken the effort to put in place modern quality tools. That was new, and was stated in the EU regulation. There is an agreement on the intent that there would be flexible regulatory approaches to encourage innovation.

I think you heard from Emer [Cooke] about the 2010 variations regulation and the recently-issued Q&As in March, 2012 – great efforts from the EU side.

Within FDA a few years ago there has been discussion about the concept of CMC post-approval management. I thought while I was at the FDA, and now as well, that it provided a unique opportunity. There are two features in that concept that was discussed a few years ago that are essential for us to address today. Otherwise I will argue that we will not make significant progress.

The two key features are, number one, clarity on the regulatory commitment. Industry needs to know what information provided in the application is considered a regulatory commitment. Without that, we will never have regulatory transparency. There will always be a desire to put in as little information as possible. Is this the right approach? I hope not.

The second key feature…is the following: Demonstrated process and product understanding and control could lead to significant reduction in post-approval manufacturing supplements. That means that the more you know the more the agency trusts the manufacturer to manage many of the changes without regulatory approval.

These are the two key features of the argument. Without having clarity on what the regulatory commitment is and rewarding innovation, no progress will be made. Initial progress was made…based on existing regulations – no new regulations were needed. But implementation progress was stopped later on.

**GSK Experiences**

I want to share with you some specific GSK experiences, but I will be brief.

In the post-approval protocol area within the US, I think we have very limited experience. There is a lack of understanding from industry about the expectations. And I think that…we do not have a current draft of an FDA comparability protocol. The previous version of the draft was issued ten years ago.

We have had more successful experiences in the EU, especially in the area of biopharmaceuticals. We have several post-approval change management protocols that have been approved in Europe…. In one case, the drug product was a lyophilized powder for intravenous injection. We wanted to purchase an additional site. And with sufficient information, GSK’s proposal was approved in the EU.

There was a similar one in which the manufacturing process was not changing, but we were scaling up and looking for another site to meet market demand. That change was also approved. I think the EU having more detailed information on the comparability protocol supplemented by the Q&A in March has been very helpful.
Moving Forward

So having this background, how can we move forward? I think there is an opportunity to really make a significant change, and in order to do that I will become a little bit more clear, visiting the desired state, the current challenges, and make some specific next steps.

I thought about coming up with a new ‘desired state,’ but there is no reason to confuse everyone. So I started with Janet Woodcock’s desired state…. But what I decided to do is to provide my interpretation of the desired state.

My interpretation of Janet’s description of the desired state is that industry is responsible for development and manufacturing, continuous improvement and quality. Industry should become more innovative than it is today. Efficiency and flexibility are needed to assure availability of necessary medicines and for industry to be competitive.

There is a need for appropriate regulatory oversight. That is easy to say. However, excessive regulatory requirements can drive unnecessary activities of both industry and regulators. And industry is reluctant – and this is a fact – to adopt new technologies for two reasons. Some are business reasons, but in addition to that, the perceived regulatory risk and regulatory cost.

Can you imagine a global pharma company making a change and the need to file changes in hundreds of countries to meet hundreds of different regulations? It is very difficult and very costly. That is why the easy way is not to do it.

Challenges and Opportunities

There is a lack of clarity of regulatory expectations. The level of detail in the regulatory submission and the reluctance to share information is a fact. How to leverage enhanced product and process understanding to achieve operational flexibility? I will argue here that learning from the previous approach and the FDA CMC post-approval management concept can be helpful. It does not have to be the same, but the idea itself is helpful.

I think the lack of harmonization within and outside ICH is a big problem. There is increasing divergence in the emerging market requirements, with every country coming up with its own regulations. It makes it at times more difficult to the perception that there is more quality.

In the EU and the US, there is no clear mechanism for describing the details of what it is that you want to register or what the regulatory commitment is. I know some people don’t want to hear that, but it is a fact. We need to know what part of the hundreds and thousands of pages in the regulatory filing is considered a regulatory requirement.

I will argue that in Japan there is an approach that describes what they consider to be a matter subject to approval. I think that is very much in alignment with the concept of CMC post-approval management.

A risk-based approach to CMC review was agreed upon in ICH Q8, Q9, Q10 and Q11, but I think we need to make a distinction about: ● what information is needed for approval versus additional information that is supportive in nature ● change management and robustness of internal processes that allow and require trust of manufacturing managing many of their changes without regulatory approval, and ● the role of the reviewer and inspector and what to be submitted and to be evaluated during inspection. The concept of a CMC post-approval management plan is helpful.

A Way Forward

The key questions that I will argue as I did a few years ago…is that these are questions we need to address in order to get to the root cause and fix the problem once and for all. Going forward, I would argue that there is a need to simplify and clarify regulatory expectations. One way to do that is to focus mostly on control strategy. Global harmonization of regulatory standards is important.

I see that there is an interest now in what some people consider one global submission – that one submission will be sufficient for the entire world if it meets some rigorous and robust internationally-recognized quality standards. We need a robust change management system to assure quality and facilitate innovation and continual improvement.
Based on that, I really see that there are two big ticket items: one is the control strategy, and one is change management. I could spend a few hours on each, but what I have decided to do is to spend one slide on each.

Control strategy is defined in ICH Q10 and is based on development approaches – QbD or anything else you desire – and the desired manufacturing and operational flexibility. A greater assessment of the role of control strategy needs to be done jointly by review and inspection.

What I am trying to advocate and stimulate some discussion on is that control strategy – since it is the key regulatory part of the filing to assure quality, safety and efficacy – should serve as the primary regulatory commitment. Additional information needs to be there for transparency and to share the science, but it should be there as supportive information intended to facilitate the review, assure fitness for use, and robustness of the control strategy.

ICH Q10 provides a reasonable foundation for change management under a pharmaceutical quality system. I would argue, and I think there is some support that I heard today, that harmonized technical criteria need to be established for change management. All efforts so far –regional or global – have been to address the regulatory process and the types of changes and how to report them. There has not been a significant effort to focus the discussion toward the development of a guideline on the evaluation and effect of changes on quality, safety and efficacy. I think an ICH guideline in this area would be very helpful.

The regulatory processes and regional requirements will stay there for a while. There are different requirements in most markets within and outside ICH. The question is, ‘if we become successful and there is an agreement among industry and regulators to develop a guideline on technical criteria for change management, is it possible to meet different regional requirements with one set of technical standards?’ I think that has to be part of the discussion.

Suggested Next Steps

I have some specific suggested next steps.

- Number one: I think we have lots of experience now with QbD and the ICH guidelines, and global cooperation. I think it would be useful to have a joint session between industry and regulators to address the following issues: technology; optimum format for control strategy, among other things; and the future needs – whether we need additional guidelines or if we have enough so that there is no need to do that. We need open, frank and candid discussion about where we are and where we need to go.

- Number two: I personally think there is a need for two major harmonized guidelines – one on control strategy and one on risk- and science-based thinking criteria for change management. I sense some degree of support here in this room. I think these key two features in the FDA concept of CMC post-approval management need to be considered.

I conclude that the current system is challenging to industry and regulators. New guidelines and regulatory initiatives have provided only marginal benefits, at most. A simplified post-approval framework that focuses on quality and safety is urgently needed. The FDA CMC post-approval management plan concept, or another modified, updated version of it, would be helpful. A harmonized guideline on control strategy and technical criteria for change management are urgently needed.

While we are doing all this discussion I think it is important for us to think about the bigger picture. The bigger picture is not guidelines or change management, it is the patient. High-quality pharmaceuticals are needed to improve the quality of life – I think we can all agree to that. Effective dialogue and collaboration between industry and regulators is crucial to support innovation and continuous improvement. The availability of high-quality medicine is a shared responsibility. What is needed now more than ever before is bold leadership, necessary to meet the 21st century expectations – not to make minor changes on 25-year-old guidances.
**Updates in Brief**

**BRIEF:** Alleged Use of “Gutter Oil” to Produce Antibiotic Intermediate in China Probed

The government of Central China’s Jiaozuo city sent a team in early September to a subsidiary of Joincare Pharmaceutical Group to investigate allegations that the firm is manufacturing an antibiotic intermediate using reprocessed cooking oil, called “gutter oil,” China Daily reports.

China’s State Food and Drug Administration (SFDA) announced that it would investigate the truth of the media reports as well.

“Gutter oil” refers to reprocessed oil made from kitchen waste dredged from gutters behind restaurants. The substance has been the focus of several food safety scandals in China after it was found to be illegally reused by restaurants or bottled for sale.

Chinese media reported in early September that a subsidiary of Joincare Pharmaceutical Group located in Jiaozuo purchased the “gutter oil” and used it to produce the widely used antibiotic intermediate 7-amino cephalosporanic acid, or 7-ACA. The firm is alleged to have blended the oil with soybean oil that is used in the manufacture of 7-ACA.

7-ACA is used as a final intermediate in the production of a number of cephalosporin antibiotics. Joincare produces 25% of total the amount of 7-ACA used in China, according to media reports.

Joincare released a statement on its website refuting the media’s reports and said it was willing to accept the government’s supervision and inspection.

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