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Bill Paulson, Editor-in-Chief

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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CBER Focus Intensifying on Export Certification, Adverse Event Databases, and Lab Help in Product Development

Initiatives that will be on the front burner at the Center for Biologics Evaluation and Research (CBER) over the next year include: ● the completion of an electronic export certification system ● the increased use of databases to identify and confirm adverse events with vaccines and blood products, and ● using its extensive laboratory facilities and expertise to help in the development of novel products.

CBER Office of Compliance (OC) Director Mary Malarkey emphasized the significance of CBER’s soon-to-be-launched Biologics Export Certification Application and Tracking System (BECATS) in providing an update on her office’s initiatives at the annual PDA/FDA conference in Washington, D.C. in mid-September.

Firms exporting products from the US are often asked by foreign customers or foreign governments to supply a “certificate” for products regulated by FDA – a document prepared by the agency containing information about a product’s regulatory or marketing status.

BECATS aims to streamline the process for applying for and obtaining export certificates for CBER-regulated products using an all-electronic Internet-based form of submission. Malarkey noted that the first phase will address certificates for foreign governments, which accounts for about half of CBER’s certificate workload. She anticipates a roll-out “very shortly.”

Other current CBER OC focal points, Malarkey said, include: ● the implementation of FDASIA ● flu vaccine and pandemic preparedness ● an electronic lot release system ● a direct recall classification system ● risk-based efforts to focus inspection and compliance resources ● updates to its website, and ● the center’s upcoming move to FDA’s White Oak campus. She also commented on the “large inventory” of facilities that CBER oversees and the compliance actions the center has been taking recently.

Adverse Events, Lab Research Among Top CBER Priorities

Giving a center-level review of initiatives at the concluding session of the PDA/FDA conference, CBER Deputy Director Peter Marks commented that the “most significant” activity that the center as a whole will pursue in the next year is the use of “large databases” to analyze adverse events with the products that it regulates.

“We are trying to identify signals and then confirm them using things like the Sentinel database, which now has more than a million records, along with other large databases,” Marks explained. He emphasized that the effort “is not simply a fishing expedition” – that Sentinel and other database initiatives “are based on rigorously-designed...
protocols with very strong statistical methodologies used both for signal identification and signal verification.”

The database work at CBER is being pursued in its Office of Biostatistics and Epidemiology. Also under exploration is the use of social media and text mining for the collection of adverse events.

CBER’s research laboratory component – one of the largest at FDA with several hundred scientists – is prioritizing activities that will help in the development of novel products.

Marks pointed to the resurgence over the past year in incidents of whooping cough. He attributed the resurgence to a combination of fewer people getting vaccinated against pertussis and the possible lack of effectiveness of the current vaccine as compared with the previous vaccine, “which was associated with more adverse events.”

To help tackle this problem, CBER scientists have developed a non-human primate model that “should help” facilitate further vaccine development. “That is something that we can uniquely do with our resources that others might not do that benefits product development,” Marks emphasized.

Small Center, Big Job

Malarkey pointed out that although CBER is a relatively small center, it has a “large inventory” of establishments to cover and performs a lot of work in the epidemiology and biostatistic areas with blood bank and flu vaccine data.

In addition to the drug and device facilities it covers, CBER is also responsible for over 2000 blood banks and more than 3000 human cell tissue and cellular tissue-based product facilities.

“It is quite an inventory,” she commented, “and we need to think smartly about how to best cover that and ensure the safety of those products.”

Regarding her center’s work with the quality of flu vaccines, Malarkey noted that “now we have so many more flu vaccines, which is terrific. But it also means that our preparations to get ready for the year are much more intense because we have a lot more reagents and standards to prepare.”

As with all FDA centers, the implementation of FDASIA is also taking center stage at CBER.

Malarkey explained that her group is working with colleagues in CDER and ORA and other parts of the agency in achieving the FDASIA goals – in particular, provisions of the prescription drug and medical device user fee acts (PDUFA and MDUFA) in the context of the drugs and devices that CBER regulates.

In that regard, Malarkey pointed to the importance of getting complete submissions. “Because of some of the new requirements, we simply have to do more review of the file if we do not get complete submissions. We are relying on you to make sure that happens so that we can meet all of our goals under these new programs.”

CBER’S MARY MALARKEY ON COMPLIANCE OFFICE INITIATIVES

At the PDA/FDA conference in mid-September, CBER Office of Compliance Director Mary Malarkey provided an update on the initiatives her office is currently undertaking and discussed the growing dimensions of CBER’s establishment inventory and some compliance activities that the center has been taking recently.

Over the next few minutes I would like to present some of what we are doing in CBER compliance – our priorities, our initiatives. I know that the later session this morning features the center directors, so I will focus on the activities in our compliance office.

I will talk about our organization, mission, and current priorities. Some of the initiatives that we have in place are on the webpage. I will discuss something called BECATS. Then I will finish up with just a few compliance action updates that are relevant to this particular audience.

Office Structure

Starting with the current structure [of CBER’s Office of Compliance and Biologics Quality (OCBQ)]: For those of you not familiar with CBER, we are not a super office yet, but we have super people. We have four divisions:

- Inspection and Surveillance, which I think is self-explanatory – they work very closely with our colleagues in ORA [the Office of Regulatory Affairs]
- Case Management, which is where all the cases are managed…
● Manufacturing and Product Quality, and

● Biological Standards and Quality Control. It is actually an ‘Essential Regulatory Laboratory’ [ERL] under the WHO – one of four in the world. So we do lot release testing and preparation of standards and reagents to ensure the safety of products around the globe.

Our mission in OCBQ is to ‘ensure the quality of products regulated by CBER over their entire lifecycle through pre-market review and inspection, and post-market review, surveillance, inspection, outreach and compliance.’

**Priorities**

**Implementation of FDASIA**

We are working with our colleagues in CDER and ORA and other parts of the agency in achieving the goals that Congress has set out for us. We are thankful for the additional legislation. Some of this is around PDUFA V and MDUFA III, because we regulate devices as well.

I just want to put in a plug for the need and the importance of getting complete submissions. Because of some of the new requirements, we simply have to do more review of the file if we do not get complete submissions. We are relying on you to make sure that happens so that we can meet all of our goals under these new programs.

We have focused a lot on Title VII, which is on the supply chain [see IPQ “Monthly Update” September 2013, pp. 24-39; May 2013, pp.16-22], and Title X [see IPQ “Monthly Update” March 2013, pp. 2-8; October 2012, pp. 4-13], which is on drug shortages. We are participating with our colleagues. All of the updates on the progress with the various titles are available on the FDA website.

**Move to White Oak Campus**

We are moving to White Oak – which is a big deal – and we are looking forward to it, to be with our colleagues. But getting ready to move takes a lot of time and energy, particularly for our lot release laboratories and our filling suite.

**Flu Vaccines**

I mentioned the flu yesterday. I talked about the flu shortage back in 2004-2005, and the fact that now we have so many more flu vaccines, which is terrific. But it also means that our preparations to get ready for the year are much more intense because we have a lot more reagents and standards to prepare.

This year we have had two strain changes. As folks know, there are generally three strains in a flu vaccine, any of which could change. But this year we also have quadrivalent vaccines with two B and two A strains. Then, of course, we have two new cell-based vaccines, one in insect cells, and the other more traditional cell-based. There is a lot going on and that is a wonderful thing – it is more products available for everyone. But again it puts us and our colleagues and the other ERLs in quite a position of work.

There is also continued vigilance around emerging strains. The H7N9 that appeared in China earlier this year is of particular interest to the United States government and we are working with our colleagues in the government and our foreign colleagues as well to prepare for that in case it should turn into something more than what we are seeing now.

**Lot Release and Recall Classification Systems**

We are continuing the expansion of the **electronic lot release system**. And I am just putting in a plug that when we call you, and you do have lot release through CBER, that we would love for you to participate. It makes it easier on all of us if this can be done through the electronic gateway. We only have ten manufacturers right now with twelve products that are participating, but we hope to expand it, and we are continuing to work with the industry to do so.

We completed the implementation of the **direct recall classification system**. This is now up and running for all CBER-
regulated products. There have been outreach efforts at a number of fora around this. There is a lot of information on our website about how this works – it actually streamlines the process and makes it more timely for everyone.

**Resources and Establishment Inventory**

We continue our risk-based efforts to focus inspection and compliance resources. This is something we have been doing for years. But of course now FDASIA has made it even more apparent that that we need to look across the board at our data when we do these approaches. And we work closely within CDER and with our colleagues at ORA to accomplish the public health goals that we have.

People do not think about it, but we have quite a large inventory ourselves. We have over 2000 blood banks, and over 3000 human cell tissue and cellular tissue-based product establishments in addition to our drug and device facilities. It is quite an inventory, and we need to think smartly about how to best cover that and ensure the safety of those products.

**Website**

We launched a new website that I will talk a little bit about. It is meant to be one-stop-shopping for all of you, so you do not have to bounce around. I think we at FDA have all heard the stories about people going to Google instead of our website because it is a lot easier to find things. So we are trying to do what we can to make it more user-friendly. This is our stab at that. You can find the guidance documents that might be most relevant to what you do.

Our new web page was posted in April. It is an overview of our office. It breaks things down by division and the various guidance documents and SOPs that would be relevant to that division. We have direct links to the most relevant documents. We hope that it will be something that will be useful to you. This is just a screen shot, and you can actually get to this from the main CBER page if you click on ‘guidance and compliance.’

Just another screen shot of various divisions: For example, if you click on the division of case management you are going to hear about imports and exports, and you are going to hear about recalls, because that is the division that handles those particular topics…. We would love your feedback. We are trying to monitor the hits that we get and see if we can adjust accordingly.

**BECATS**

We will soon be launching the Biologics Export Certification Application and Tracking System, or BECATS. We are actually piggy-backing on an existing system. We do issue export certificates, and this will help streamline that. We get a lot of requests from many of you, and we would encourage you to use this once we have it available. We are hoping to have it available on October 1st.

BECATs, as I mentioned, is an Internet-based form of submission. It is all electronic. We skip the faxes and paper documents.

Our first phase will be the certificates for foreign governments, which is about 50% of our certificate workload. And we do anticipate, as I mentioned, a roll-out very shortly. You will see that in our email reminders about things and we hope to add additional certificate types over time. If you have folks in your shops that regularly come to us and ask for such certificates, they will find that this is a new way of doing business that will hopefully make it a lot easier for all of us.

**Recent Compliance Actions**

**GMP**

Finally, I will talk a little bit about some of the compliance actions that we have seen. With our inventory of drug providers – which is not as large – we do not see a lot of activity, which is good. Here we have, as of the end of August, the number of warning letters and untitled letters [one warning letter and four untitled letters year-to-date as of mid-August, FY2013]. We have had somewhat of a surge of untitled letters recently. You can see that there are not a lot of warning letters.
Our focus has been more on the HCTP area, the human cell tissue and cellular and tissue-based product area. These products can either be regulated solely under section 361 of the Public Health Service Act, or if they do not meet certain criteria...they are generally going to be drugs, devices, or biologics.

As they are cellular, we have seen more issues with aseptic processing. That has taken the number one spot in our citation breakdown over the last year. I think for many years it had been 211.192 – the lack of thorough investigations and identification of root cause – that had been number one. But now we are seeing a little bit of a change because of the inventory that we are looking at.

We also are seeing issues with having actual scientifically-sound specifications for some of these products and for a lack of process validation, as well as a lack of investigations, and actually using products that do not meet specifications.

The statutory GMP citations that we have seen are pretty consistent with that – with production process controls and microbiology control now number one, with failure of investigations and control of components coming thereafter.

**Internet Actions**

Finally, we are always looking at the Internet. This is a breakdown of the actions that we have taken [● seven letters issued 4/3/12 to sites selling SD Bioline HIV 1/2 (version) 3.0 test to American consumers ● another letter issued 4/17/12 for a different kit, and ● two letters issued thus far in FY13.] The numbers are small. And unfortunately when we take the actions what happens is that they pop back up somewhere else. But we do try.

One of the areas that we have focused on for years is sites promoting unapproved HIV home test kits. This is a serious issue where people are given the impression that if they order these kits they are going to give them a real result. But they do not work. So we are consistently going after these sites. It is kind of like ‘whack-a-mole’ – you whack them down and they come back, unfortunately.

The good news is that now we do have a home testing kit that is approved for home-use as well as the home access test kit, which has been on the market for years and allows for you to send blood samples to a laboratory. So there are other options available that are FDA-approved and we continue trying to make more available to the public.

And finally, it is not unusual when we have problems with flu vaccine – whether it is a shortage or a new strain or something – that we also get the Internet flu people who come and say, ‘hey, we have got the cure for you’ or ‘hey, we have a substitute vaccine.’

And you may remember it was kind of a late season last year, or I should say kind of an early season that popped up, but a late season for vaccinations. Everybody that did not get vaccinated all of a sudden wanted vaccine in December and it was a little late in the season to get one. So it was kind of a panic. Just a little bit of a panic is all it takes for these Internet folks to come out.

In February, the agency issued nine warning letters, including three jointly with our colleagues at the Federal Trade Commission. One of the firms claimed to be an alternative for flu vaccine, so we were intimately involved with that. We did have a website posting to bring to people’s attention that these are fraudulent products – they are not approved or cleared. We try to keep up with this as much as we can.

**CBER Vision**

I would like to leave you with our vision for CBER: [CBER uses sound science and regulatory expertise to: ● protect and improve public and individual health in the US and, where feasible, globally ● facilitate development, approval of and access to safe and effective products and promising new technologies, and ● strengthen CBER as a preeminent regulatory organization for biologics.]

We have a very good staff at our office of communication, outreach, and development that can help you and direct you where you need to be at CBER.
Register before October 29 and save.

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Comment Process on FDA’s Proposed Rule on Product Detention During Inspections Reflects Industry Support

The comment process on FDA’s proposed rule on “Administrative Detention of Drugs Intended for Human and Animal Use” as authorized under Title VII of the FDA Safety and Innovation Act (FDASIA) has indicated industry’s comfort level with extending the detention authority the agency already had for foods and devices to drug products.

The proposed rule provides the agency with the ability to detain products if inspection findings raise red flags and is one of the components in the FDASIA toolbox designed to strengthen FDA’s ability to keep substandard drug products out of the supply chain. To date, the only enforcement option the agency had to forestall product distribution was the slower and more cumbersome seizure pathway, which required court involvement and has been increasingly sparsely used.

The draft rule was originally released in early April with a 30-day comment period, but FDA did not receive any industry feedback and only one “nonsubstantive” comment. It was re-released in mid-July – this time with a 60-day comment period – in the hopes of drawing more meaningful industry feedback. The second request for input drew four industry responses: One from a big pharma company – Novo-Nordisk; and three from associations – the Biotechnology Industry Organization (BIO), PDA, and the Generic Pharmaceutical Association (GPhA).

The relatively small number of comments that the draft rule has drawn and the substance of those comments indicates industry’s recognition of the vulnerability of the drug supply chain and the need for more regulatory tools to help protect it.

Novo affirmed that it “welcomes any measures intended to keep adulterated and misbranded pharmaceuticals out of the supply chain and ultimately away from patients.” BIO emphasized that it “appreciates the timely release and comprehensive nature” of the proposed rule as well as “the agency’s effort to ensure regulatory ease and efficiency, as the proposed rule closely follows the administrative detention paradigm already in place for other FDA regulated products.”

While GPhA indicated that it had no specific comments “at this time,” the association stressed generally that it believes “FDA is the only regulatory body qualified to make the public health decision on administrative detention,” and that it supports the agency’s “efforts to work towards the development of a clear and proven guidance.”

Anatomy Of a Legislative Success Story

The general acceptance of the new regulation by industry reflects the sentiments of Congress when the legislation mandating the rule was drafted and passed.

During a public meeting held by FDA in July to get input on its Title VII implementation strategy, Keith Flanagan, a former senior counsel on the Senate Health Education Labor and Pensions committee who co-authored the FDASIA legislation, explained that the supply chain provisions had wide bipartisan support in Congress.

At the meeting, Flanagan provided an insider’s view of the history of the legislation and how both houses of Congress came to agreement on what authorities to give to FDA to better protect the drug supply chain. He joined FDA in early 2013 as a senior regulatory counsel in FDA’s Office of Regulatory Affairs to help implement the legislation that he had played a key role in shepherding.

Flanagan pointed out at the FDA forum that the bill passed in the Senate by a vote of 96 to one, and the House version, which “closely mirrored” it, also passed by a wide margin.

Although conference discussions between the chambers on other FDASIA provisions “sometimes involved hard bargaining and reciprocal concessions,” he noted, “there was very little horse trading concerning Title VII issues. Title VII was not that controversial.”

The lack of a level playing field in the international inspection arena has been a bone of contention among domestic manufacturers for many years, and the FDASIA effort to help address the problem received substantial support and participation from industry and FDA proponents.

Although the bill had strong bipartisan support, congressional staff faced significant challenges due to the difficult legislative environment in 2011 – a period when almost no bills of significance were being passed.

In addition, the supply chain provisions were attached to broader legislation that included user fees, for which hard statutory deadlines were operative. The result was that points of significant contention from stakeholders had to be either quickly resolved or deleted from the bill to ensure its timely passage.
Flanagan cited FDA topsider John Taylor, Amgen and Rx-360 exec Martin Van Trieste and Pew Trust’s Alan Coukell, in particular, who were also presenting at the July forum, as having contributed “very significant amounts of time and expertise to the development of this legislation” and being “very important influences in the process.”

[Editor’s Note: Flanagan’s full remarks on the FDASIA drafting process are provided below.]

**Detention Complements Other FDASIA Tools**

The draft rule enables an FDA investigator, with the approval of the applicable district director, to administratively detain drugs encountered during an inspection that the investigator has reason to believe are adulterated or misbranded.

The authority is intended to protect the public by preventing distribution or subsequent use of the drugs until FDA has had time to consider what further enforcement action is appropriate.

In addition to general provisions, the proposed rule contains sections covering:

- criteria for ordering detention
- detention period
- issuance and approval of a detention order
- labeling or marking a detained drug
- appeal of a detention order
- movement of detained drugs
- actions involving adulterated or misbranded drugs
- detention termination, and
- recordkeeping requirements.

The rule is a third component in FDA’s recent effort to move forward in the implementation of the Title VII supply chain provisions.

A companion guidance on “Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection,” driven by section 707, was released at the same time as the proposed detention rule. The guidance has drawn some industry concern regarding the degree of subjectivity it affords investigators in determining when the lines have been crossed. On the other hand, industry has also been expressing support for the agency’s effort to strengthen its ability to conduct meaningful inspections and deal with firms that intentionally try to stymie its efforts (see IPQ “Monthly Update” September 2013, pp. 29-38).

A draft guideline on implementation pathways for FDASIA section 713 on drug admission standards and 714 on registration of foreign importers and good importer practices (GIPs) was released in mid-June for a 60-day comment period. Feedback from industry centered around:

- confirming a manufacturer’s state of compliance in advance of its product entering the US, and
- establishing a risk-based tiered system with correspondingly different documentation requirements for each tier (ibid., pp. 24-28).

**Subjectivity and Patient Access of Concern**

As with the inspection obstruction guidance, one area in the proposed rule on which the industry commenters want to see clarification is the criteria agency investigators will use in making a detention decision. It was suggested that the determination should be risk-based in view of the potential impact detaining drugs could have on market supply and patient access.

Novo noted that “most drug shipments are fully legal and very much needed by patients,” maintaining that FDA “should only detain shipments based on a pre-determined, justifiable level of suspicion that determines which and how many shipments to detain.”

Similarly, BIO pointed out that the term “adulteration” is broad, and that the circumstances leading to the application of the term need to be better defined.

Both suggested that the decision to label a product adulterated or misbranded should be risk-based and applied such that the potential for drug shortages resulting from a detention is minimized.

Novo acknowledged the “severe risk” of adulterated or misbranded drugs entering the supply chain, but maintained that “the means to mitigate this risk should be proportional to the risk of interfering with the crucial supply of legal drugs to patients.”

BIO recognized that the proposed rule “does attempt to ensure that administrative detention is used only as necessary and appropriate by requiring prior approval by the FDA District Director.” However, the association suggested that the detention standard “include an element of potential risk of public harm…to ensure that the rule as implemented fully reflects the intended policy purpose of protecting public health, which also includes ensuring patient access to medicines.”

BIO also pointed to the “multivariate interaction” the proposed rule has with the agency’s draft guidance on obstructing inspections. In both the guidance and the rule, the association maintains, “drug product can be labeled adulterated/misbranded, and thus withheld from patients without due process.”

“Without due process or acknowledgement of risk/benefit considerations for patients, unnecessary drug shortages may occur,” the biotech association maintained. “Clarity” in both the draft guidance and the proposed rule is “essential to limit variability in interpretation by the district investigators.”

PDA also weighed in on the access issue by
suggesting that the rule be amended to ensure that the notification to a firm when a detention is lifted be as rapid as possible.

“Rapid notification,” PDA maintained, “is key to minimizing potential risk to patients caused by a delay in the availability of product. For short shelf life products, a matter of days can have a significant impact on ability to maintain the highest standards in the product quality.”

**Detained Product Storage, Foreign Application Addressed**

Both BIO and Novo raised concerns with: ● the handling, movement and storage of detained drugs, and ● maintaining product quality during detention.

Novo pointed out that “when the agency does detain a shipment, the detention should not impact product quality, i.e., storage and handling of detained products should be in accordance with the requirements stated by the manufacturer.” The firm also recommended that FDA should “immediately” notify the party responsible for a detained product “to avoid any mistakes or misunderstandings [and to] enable product owners to inform customers that their orders may be delayed as well as opened and checked by FDA.”

Reflecting “the unique nature of biologics and required environmental controls such as cold-storage,” BIO asked that the agency amend the guide with language reflecting assurance that “there is appropriate flexibility for movement of detained drugs outside of the establishment/facility (e.g., to an approved storage facility) in order to preserve product integrity while in the detention process.”

PDA suggested that the principles of the guidance also need to be extended to foreign inspections.

The association requested that the following language be added: “If FDA determines drugs manufactured at a non-U.S. site may be adulterated or misbranded, FDA will notify and cooperate with the local health authority to ensure protection of the public health through notification in the spirit of international cooperation.”

It further suggested that the preamble to the final rule should, “if possible, denote the manner in which it will work with foreign governments to address concerns noted at foreign facilities.”

**DOWNLOADS FROM THE STORY:**

- Administrative detention draft rule
- Comments on the draft rule submitted by:
  - BIO
  - GPhA
  - Novo Nordisk
  - PDA

**FDA’S KEITH FLANAGAN ON THE LEGISLATIVE HISTORY OF FDASIA**

During FDA’s July Title VII implementation meeting, Keith Flanagan, who in his former role as senior health counsel on the Senate Health Education Labor and Pensions committee co-authored the FDASIA legislation, provided an insider’s view of its history and how both houses of Congress came to agreement on what authorities to give to FDA to better protect the drug supply chain. He joined FDA in early 2013 as a senior regulatory counsel in FDA’s Office of Regulatory Affairs to help implement the legislation that he had played a key role in shepherding.

It is a special privilege to be able to work on the FDASIA implementation. I have to start with some caveats and qualifiers. As mentioned, I am not speaking on behalf of FDA today. And although the agenda says ‘Congressional Perspective on FDASIA,’ I am not speaking on behalf of any member of Congress or anyone in Congress right now. Rather because I co-authored the bill I can provide some context on how FDA got these authorities.

I will briefly walk you through the public record and share a few personal experiences for the purpose of providing a little context. It is also hard to go after several of your colleagues because a lot of material has already been covered so I am trying not to be repetitive.

As many prior speakers noted, the story of FDASIA Title VII arguably starts with the heparin tragedy... In the months and years that followed, congressional committees, the Government Accountability Office, and others investigated and made very strongly critical findings.

In 2009, representative Dingell introduced the FDA Globalization Act, intended to upgrade FDA’s authorities to cope...
with globalization across product lines. One of Congressman Dingell’s lead advisors at the time was Jeannie Ireland. She is now a senior advisor to Commissioner Hamburg and recently served as FDA’s associate commissioner for legislation.

Also in 2009, Senators Kennedy and Grassley introduced the Drug and Device Accountability Act, or DADA, a bill concerning medical product supply chain safety. David Dorsey, who formerly served as FDA's acting associate commissioner for policy and planning, was on detail at the time to Senator Kennedy’s staff, and took a leadership role in developing the bill. Parenthetically, there was some speculation that the acronym DADA may have had some relationship to Mr. Dorsey’s status as a new parent.

In 2010, Senator Bennet of Colorado introduced a bill focusing on drug supply chain integrity. Then, as [Counselor to the Commissioner and Acting Deputy Commissioner for Global Regulatory Operations and Policy] John Taylor referenced, the PEW Charitable Trusts in March 2011 held a stakeholder conference concerning globalization of the pharmaceutical supply chain. John Taylor, [Amgen VP and Rx-360 Treasurer and Past Chair] Martin Van Trieste and [Pew Charitable Trusts Senior Director, Drugs and Medical Devices] Alan Coukell, all of whom are speaking here today, were among the participants. The conference sort of highlighted emerging consensus and the need to take legislative action.

As John also mentioned, in 2011 FDA released its pathway report and in July 2011 Commissioner Hamburg was the sole witness at a Senate health committee hearing concerning user fee legislation. The only thing she asked for other than the user fees was new authorities to cope with globalization of the pharmaceutical supply chain. The Hill staff definitely took notice.

In September 2011, in a hearing in front of the same committee, former Deputy Commissioner Autor said it is not a question of if, but when we have another heparin incident, and that FDA needs these authorities. Accordingly, the Senate health committee chairman Harken made drug import safety his top priority for the user fee reauthorization. PEW and other public interest groups strongly supported him and the industry liked the idea of leveling the playing field for domestic manufacturers.

These issues were also important for House Energy and Commerce Committee members. House investigators had to devote considerable time and energy to heparin issues. In short, there was bipartisan interest in Congress, strong support from stakeholders and strong support from FDA itself to tackle these issues.

Having said that, the Hill staff faced significant challenges. First, the legislative environment was difficult. A June 2011 Politico article cited the statistic that just 18 bills had become law through the first half of 2011, and 15 of those named a building after someone, temporarily extended expiring laws, or appointed an official to the board of the Smithsonian Institution. It was a difficult time to try to legislate.

Second, we had a hard statutory deadline: We needed to reauthorize the drug and device user fee program by the end of September 2012 in order to avoid layoffs and substantial disruption at FDA. Given these and other challenges, Hill staff strategy was to develop a policy consensus. If anyone strongly objected to a policy proposal, it was removed from the bill. A senior Hill staffer referred to this as ‘the hair on fire test.’ If a provision set anyone’s hair on fire, and could not be fixed, we removed it from the bill.

In the Senate, a bipartisan working group comprising staff from the offices of Senator Harkin, Bennet, Whitehouse, Enzi, Burr, and Grassley reviewed prior registered proposals including the Dingell, Kennedy Grassley and Bennet bills, met with any stakeholder group that requested a meeting, and developed discussion drafts to solicit comment. When we received feedback, we worked with all affected stakeholders to try to find common ground. The trade associations, individual companies, public interest groups, FDA staff, and other stakeholders devoted many hours to the team effort.

Much of the senior career leadership of the agency, including John Taylor, Deb Autor, Steve Solomon, Jennie Ireland and Pete Beekman, visited the Hill for numerous, lengthy discussions and answering any and all questions from dozens of inquisitive staffers.
The key thing to understand about Senate procedure is that any single senator can derail forward progress on a bill. I cannot emphasize enough that throughout the process if anyone raised strong concerns we had no choice but to address them. Otherwise, we risked not getting the bill done on time.

In May 2012, the Senate passed the bill by voting 96 to 1. Also in May, the House Energy and Commerce Committee reported out its bill. Its drug supply chain provisions closely mirrored the Senate.

Conference discussions between the chambers sometimes involved hard bargaining and reciprocal concessions, but there was very little horse trading concerning Title VII issues. Title VII was not that controversial. The bill produced by informal discussions between the chambers passed the House by voice vote – that is by acclamation – and then passed the Senate by a vote of 92 to 4. The additional ‘no’ votes in the Senate this time were not prompted by the Title VII issues we are discussing today.

In summary, the heparin crisis prompted a lot of work by a lot of people at FDA, in Congress and in industry, and among a wide range of stakeholders over many years. As John Taylor pointed out, the bill does not contain everything FDA asked for in exactly the way FDA asked for it. But in general, FDASIA Title VII represents a consensus approach to globalization of the pharmaceutical supply chain.

And a brief remark about Martin Van Trieste and Alan Coukell, who are going to supplement my remarks and give a little context: Martin on behalf of Rx-360 and Alan on behalf of PEW contributed very significant amounts of time and expertise to the development of this legislation and were very important influences in the process.

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Joint Drafting of Contract Manufacturing Quality Agreements Needed to Reflect Shared Quality Ownership, FDA Stresses

FDA is stressing that quality agreements between product owners and the contract manufacturing organizations (CMOs) they work with should be drafted jointly by both parties and reflect the depth of understanding each has regarding their roles and responsibilities in the intimate relationship they share.

Lack of a well thought-out, comprehensive quality agreement, the agency cautions, is resulting in products not meeting specifications, recalls, unsuccessful pre-approval inspections, and GMP enforcement actions.

Recent GMP warning letters to both product owners and CMOs have cited concerns that could have been headed off, compliance officials point out, if the firms involved had better communicated relevant development information and delineated the specific responsibilities of each party – key building blocks of a contracting relationship in which the quality agreement plays a critical role.

[Editor’s Note: The issues around contract manufacturing that FDA has been citing in warning letters and other concerns involving CMOs have been covered extensively by IPQ, including: ● case studies showing quality agreement breakdowns ● balancing GMP enforcement with drug shortage prevention ● remediation efforts at contract manufacturers resulting from warning letters ● the impact and aftermath of consent decrees at CMOs, and ● negative inspection findings resulting from poor sponsor/contractor communications.]

The drug GMP’s state that contract manufacturers are “an extension of the manufacturer’s own facility,” and that the drug product owner’s quality unit is “responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.” While the GMPs do not explicitly require quality agreements, the agency is stressing that they are the best way to facilitate compliance with the GMP requirements that apply to contract manufacturing arrangements.

The point was underscored by CDER Office of Manufacturing & Product Quality (OMPQ) Acting Branch Chief for Regulatory Policy & Collaboration Paula Katz in discussing FDA’s new draft guidance on “Quality Agreements for Contract Manufacturing Arrangements for Drugs” at the annual PDA/FDA conference in mid-September in Washington.

Katz emphasized that “it would be difficult to engage in a compliant contract drug manufacturing operation without having a written quality agreement in place.”

Even after the guidance is finalized, she explained, investigators will “continue to inspect against the act and CGMP regulations as they apply,” and there will be “no new rules at play.” However, she commented, the guidance will provide “some clarity about our expectations.”

Quality Agreements Define Critical Roles

The guidance was released for comment by FDA in May with a comment period that closed in July.

In her presentation, Katz discussed the purpose of the guidance, its scope, and what it covers and what it does not, emphasizing that there are elements that are important parts of the larger outsourcing management program that are outside the scope of a quality agreement.

“The draft guidance really emphasizes that quality agreements should define the parties’ responsibilities, assure full compliance with CGMPs, and facilitate consistent delivery of safe and effective medicines to market,” Katz commented.

The guidance encompasses: ● human drugs ● veterinary drugs ● biological and biotechnology products ● finished products ● APIs, and ● drug constituents of combination products.

For the purposes of the draft guidance, “manufacturing” includes processing, packing, holding, labeling, operations, testing, and operations of the quality unit.

Outside its scope are medicated articles of feed, medical devices, dietary supplements, human cellular tissue/products, or activities related to business arrangements between product owners and contract facilities.

Scope Does Not Encompass Qualification

Katz noted that auditing and qualification of contracted facilities “are not issues that are contemplated by the guidance for quality agreement purposes.”

Acknowledging that auditing and qualification are part of the larger outsourcing management program, she emphasized that “the agency is aware of those things and you should be doing them as well. We just do not have a draft guidance on...
Similarly, the guidance does not cover controls that may be related to suppliers of raw materials – highlighting a distinction the agency has drawn between the purchasing of contracted manufacturing services and the acquisition of raw materials or components from a vendor or supplier.

The group that drafted the FDA quality agreement guidance chose not to employ the terminology that EU uses in its guidance on contract arrangements, opting to use “owner” and “contracted facility” rather than “contract giver” and “contract acceptor.”

The group’s concern was that the EU terminology implies the relationship is based on the giver handing over the document to the acceptor.

By contrast, FDA favored terminology that highlighted the importance of a long-term relationship in which each party participates in drafting the quality agreement and understands the expectations for how the product or products are going to be made, what services are going to be provided, and how the quality units are going to work together to get that done.

**Quality Agreement Should Stand Alone**

FDA emphasizes in its guidance, as did Katz from the podium, that a quality agreement should be a standalone document, or easily severable from a larger document it may be a part of, such that the agreement only contains quality-related information and not business-related information that FDA does not have the purview to see or need to see.

In the guidance, the agency explains that while it “does not routinely request or review business documents or business agreements on inspection, FDA routinely requests and reviews evidence of quality agreements or the lack of quality agreements.”

Referencing a presentation given at the conference by Pfizer VP Mary Oates in which she used the terms “price-agnostic” and “commercial-agnostic,” Katz commented “that is the idea. The quality agreement should be something that is discrete and separate from pricing and indemnification terms – those kinds of areas are really business and commercial.” She maintained that having a stand-alone document or one that could be severed from a larger document, such as a manufacturing services agreement, “makes it easier for you, the companies, and for us, the agency, when we come to inspect…. If you have a document that you can hand to us without spending days redacting or extracting the pieces that are particular to the quality relationships between the parties, that makes it a lot easier for you and a lot easier for us. So it is also a practical concern.”

**DOWNLOAD FROM THE STORY:**
• FDA quality agreement draft guidance

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**CDER’S PAULA KATZ ON QUALITY AGREEMENT DRAFT GUIDANCE**

At the PDA/FDA conference in mid-September, CDER Office of Manufacturing & Product Quality Acting Branch Chief for Regulatory Policy & Collaboration Paula Katz reviewed FDA’s draft guidance on “Quality Agreements for Contract Manufacturing Arrangements for Drugs.” She discussed: ● the background and legal framework for the guidance ● “takeaways” regarding: why the agency chose to use the terms “owner” and “contracted facility;” key elements; responsibilities; change control; expectations on inspection, and ● warning letters regarding quality agreements in the contract manufacturing context. In her presentation, Katz referred to the other talk given at her session on quality agreements by Pharmaceutical and Regulatory Consultant Rebecca Devine.

I will provide a little bit of background on: ● why we outsource ● the legal framework for the guidance ● quality agreements, and ● the draft guidance scope, purpose, and definitions that we use in the document, and ● a few minutes on some enforcement perspectives and potential outcomes.

I think that contract manufacturing is really a subset of out-sourcing in a very complex supply-chain. There is a distinction, at least, that we draw at the agency between manufacturing services versus things like purchases of goods, raw materials, and components. Those kinds of things are upstream, and then sort of the downstream piece is distribution of finished goods.

There are similar concepts that underlie the quality agreement pertaining to manufacturing services and a quality agreement that might pertain to a supplier. The focus is really on contract manufacturing.
Why do we outsource? Well, we see that people want things done better, maybe a little faster. Sometimes you find that a contract manufacturer has a niche expertise that you do not have yourself. You might be able to increase capacity. If you shift some resources you might have a shorter time to market. Sometimes it is an intentional temporary solution, or as a result of some other situation you may need a temporary manufacturing solution. A contractor can help you with that.

So what can contracted facilities provide? Of course, unit operations, like micronizing or sterilizing. A very big arena in contract manufacturing is contract testing – so your analytical control labs. And packaging and labeling are among a number of services that contract facilities can provide.

Legal Framework

Usually I like to provide a little bit of background on the legal framework of where quality agreements fit in. Of course, from the agency's perspective, a drug is adulterated if the methods used and facilities or controls used for manufacturing, processing, packing, or holding do not conform with CGMP. That is a phrase you should know pretty well if you are in the manufacturing business – ‘adulterated drugs.’

But a newer piece specifically links CGMP to oversight. Under FDASIA, which was enacted about a year ago, Section 711 defines CGMP to include the implementation of quality oversight and controls over the manufacturing of drugs, including the safety of raw materials, materials used in manufacturing, and finished drug products. We see this as an explicit link now between CGMP adulteration and the activities of quality management.

For reference, here are some of the regulations that we think are particularly relevant to contract manufacturing (see box at right). An important one, I think, for everyone to keep in mind, is that a contract manufacturer is responsible for CGMP just as the product owner would be. A contract manufacturer that is only doing a subset of services is only required to comply only with CGMPs that apply to those services. A packaging facility only needs to comply with packaging CGMPS. But it may not need to comply with the services it does not perform.

An important distinction between the U.S. and our colleagues around the world is that in the U.S. the regulations do not explicitly require a written quality agreement. Certainly in the EU it is required under the CGMP regs to have a written quality agreement. But here in the U.S. we do not require it explicitly in the regulations.

I would also like to point out the distinction between small molecules, biologics, and devices, for those of you involved in that arena. The latter two are more advanced and have more recent regulations than the drug GMPs. I think that they actually have done a better job in more recent years of explaining where quality agreements fit in, certainly regarding quality oversight management activities.

The drug GMPs are pretty old, as those of you who have worked with them for a while know. They have not been revised comprehensively in quite a long time. They do not make explicit that you need a written quality agreement. But we think that you could find a way to see that it is justified to expect to see a quality agreement.

The guidance sets out this argument pretty well:

### Quality Agreements: Relevant GMP Regulations

- 210.1: failure to comply with CGMPs render the drug adulterated and subject to regulatory action
- 210.2(b): if only some operations, must comply with CGMPs applicable to those operations [you can’t “contract around” CGMP!]
- 210.3(12): manufacture, processing, packing, or holding of a drug product includes packaging and labeling operations, testing, and quality control of drug products

The CGMP regulations do not explicitly require a written agreement, but the agency believes the agreement is “the best way” to comply with:

- 211.22(a): QU responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company
- 211.22(d): QU procedures & responsibilities must be in writing
- 200.10: contract manufacturers are an extension of the manufacturer’s own facility
The idea that the quality unit is responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company, and the idea that the quality unit procedures and responsibilities must be in writing. If you put these two together, the quality agreement is really a good way to facilitate compliance with these requirements.

Just some background on a previous guidance that was published prior to draft this year: The quality systems approach to pharmaceuticals CGMP from 2006. It talks about: ● outsourcing ● quality systems and quality agreements including materials and services ● specification-setting ● communication ● training, and ● harmony between the two party’s quality standards. I think that is very important.

The ICH documents also touch on the role of quality agreements. Here are some choice phrases from them for how they fit in (see box at right).

In terms of expectations and recommendations, I think another point that Becky made that is really foundational for us is that the quality agreement is part of a much larger outsourcing risk-management plan. So, as Mr. Deming said, ‘say what you do, do what you say, prove it, and improve it’. The quality agreement is just one piece in that quality management process.

As I think [former FDA compliance official, now Lachman Director David Jaworski] said this morning, ‘you can have all these great pieces in place, but the whole system may be out of whack’. We are focusing on quality agreements here, but there is a whole range of other tools in the toolkit that you need to be considering when you are talking about outsourcing, and specifically about outsourcing manufacturing.

Here are some of the other tools: ● questionnaires ● auditing ● qualification ● oversight ● report cards, and ● metrics/analytics – all those kinds of things that are sort of beyond just having a good quality agreement in place. You have to do a lot with that. And as we have said before, if it is a long term relationship, you have got to work on it. There are going to be problems. And just having a good ‘pre-nup,’ if you will, is not going to be sufficient.

Draft Guidance Takeaways

So what is this guidance about? The scope of the guidance covers: ● human drugs ● veterinary drugs ● biological and biotechnology products ● finished products ● APIs, and ● drug constituents of combination products. And for the purposes of the draft guidance, manufacturing includes processing, packing, holding, labeling, operations, testing, and operations of the quality unit.

What are not covered in the draft guidance are medicated articles of feed, medical devices, dietary supplements, or human cellular tissue/products. Importantly, qualification activities are not discussed in the guidance – auditing and disqualification of contracted facilities are not issues that are contemplated by the guidance for quality agreement purposes. Certainly we understand that they are part of the larger outsourcing management program, so the agency is aware of those things and you should be doing them as well. We just do not have a draft guidance on them. Additionally, it does not cover controls that may be related to qualification, auditing, monitoring, or disqualification of suppliers of raw materials.
As I mentioned earlier, there is sort of a distinction between provision of contracted manufacturing services and the acquisition of raw materials or components from the vendor or supplier. A similar principle would apply in establishing the quality agreement and in terms of doing qualification, auditing and oversight activities, but this particular draft guidance does not cover that. The draft guidance also does not cover distributors.

The **purpose** of the guidance is to take a small bite at outlining the critical roles that are played by both the owner and the contracted facilities to explain how manufacturers should use quality agreements to define, establish, and document their responsibilities. The draft guidance really emphasizes that quality agreements should define the parties’ responsibilities, assure full compliance with CGMPs, and facilitate consistent delivery of safe and effective medicines to market.

**Why “Owner” and “Contracted Facility” Terms?**

One topic that I know is on a lot of peoples’ minds is why we use the terms ‘owner’ and ‘contracted facility.’ Why not use ‘giver’ and ‘acceptor?’ The terms ‘giver’ and ‘acceptor’ kind of imply a role that each of those parties would play, i.e., ‘I am the giver and I am handing you a document and you are going to take it for what it is worth.’

We see this as being much more of a **two-party relationship**. We talked about a marriage. We talked about a long-term relationship between two parties who are coming together. The lawyer’s term is, ‘to have a meeting of the minds.’ You do not have to have a meeting of the minds in a lawyer’s sense for your manufacturing services agreement [MSA], but you do need to be on the same page. It is not just a matter of one party saying to the other, ‘here is what you will do’, and the other party saying ‘yes, okay’, and then moving on.

It is really about two parties who are engaging in a long-term relationship, and you understand the expectations that each of them has for the other in terms of how the product or products are going to be made, what services are going to be provided, and how the quality units are going to work together to get that done.

It was a deliberate choice to use these terms and to really step away from what might be some other concepts behind giver and acceptor in this draft guidance. Things may change. We are certainly reviewing all the comments that came in. We will see how it comes out.

In the draft guidance we also talk about a quality agreement as a **comprehensive written agreement** that defines and establishes the obligations and responsibilities of quality units of parties involved in contract manufacturing of drugs subject CGMP.

I think that Becky did a great job earlier talking about the distinction between the supply agreement or a manufacturing services agreement or a technical agreement, and what the quality agreement is. We basically expect it to be a **standalone document**. It certainly could also be part of an MSA. But it would need to be severable – something that could stand by itself. I think [Pfizer VP Mary Oates] talked earlier this morning about having sort of price-agnostic or commercial-agnostic discussions, and that is the idea. The quality agreement should be something that is discrete and separate from pricing and indemnification terms – those kinds of areas are really business and commercial.

The quality agreement should be standalone or a severable document. One reason for that is that it makes it easier for you, the companies, and for us, the agency, when we come to inspect. We want to take a look at your quality agreement. We do not want to see or have any purview over your business or commercial terms. So if you have a document that you can hand to us without spending days redacting or extracting the pieces that are particular to the quality relationships between the parties, that makes it a lot easier for you and a lot easier for us. So it is also a practical concern.

Just some food for thought from a lawyer about what your quality agreement should not be like [see cartoon below]. I certainly hope that is not your experience when you go to your [company attorney’s] office and ask them to help you with the quality agreement. But if it is, perhaps it is time for quality and legal to have a fruitful discussion about how things should proceed.
Key Elements

Importantly, the language should be really clear. As indicated by the Dilbert slide, we do not want gibberish. We want clear language to help define the key quality roles and responsibilities of each of the parties. You may not hear this from any other lawyers, but it should not be full of legalese. It should be something that you can read and understand what is expected from each party.

It should set out communication expectations and points-of-contact [POCs]. It should be clear about which product and/or services are either being made or provided. It should include who is responsible for approval of various activities. In many cases, that would be quality units. But there might be other stakeholders involved in approving different parts of the manufacturing process.

The basic sections that are covered are: ● the purpose and scope of the agreement ● the terms – by that we do not mean legal terms, but the definitions of products and services ● the term of quality agreement, which might be the effective date or the renewal or extension date, but that could also be governed by a separate supply agreement.

The phrase ‘dispute resolution’ made its way into the guidance. We do not mean formal legal dispute resolution. What we mean is when the two parties inevitably have a disagreement about who is responsible for something that you can strive to have clarity in your agreement. But inevitably there is going to be something that comes up that raises the question about how we are going to handle this problem while we are manufacturing. That is the kind of dispute resolution we are talking about – who makes the decisions and how are they elevated throughout the two companies so that the product continues to be made and be made in compliance with the requirements and is of good quality.

Responsibilities

Responsibilities should be in a separate section, and there should also be a section on change control and revisions. For me, the latter two are probably the most important elements of the agreement: Setting forth the quality responsibilities for compliance with GMP and the change in control and revisions. So I guess just a few minutes on those – who is responsible for what.

The draft guidance says that owners are responsible for final approval or rejection of a drug product to the market. That is regulation [CFR 211.22(a)]. And that responsibility cannot be delegated to a contract facility or via a quality agreement.

I have had a lot of questions about that before, so maybe I will cut them off or maybe I will stimulate them by saying this: What we mean is not that parts of the activities of reviewing batch records and things like that could be delegated, but the idea is that the final call on this product going to market or not is the owner’s responsibility. We may have discussion on that later. But that is what is meant by cannot be delegated.

Certainly the two parties should come to an agreement on how much oversight the owner may want or not want over the activities involved in making the release decision or a rejection decision. But the product owner is the party that needs to make the actual decision.

What responsibilities do the contracted facilities have? Of course, CGMPs for all the operations that they perform, and certainly prompt evaluation and addressing of any manufacturing or quality problems that are encountered. And then the contract facility should be making sure of the product disposition for each of the operations it performs.

If the owner contracts different parties throughout the manufacturing process – one party maybe does some micronizing, and then the material is moved on to another manufacturer, and someone is responsible for filling and finishing – the
quality unit there should be making a disposition decision so that the material is suitable to go on to the next step.

And then everyone is certainly responsible for compliance and for product quality. But most importantly – and this is a piece that often gets forgotten – when we are talking about two parties, maybe we should be thinking of it as about three parties. The patient is a voice who we should be thinking about in terms of the responsibilities. Everyone is responsible for patient safety.

**Change Control**

Some take-homes about change control from the draft guidance: It is important to document changes that could be implemented by the contracted facility in three different categories: ● those kinds of changes that maybe do not require any notice to the owner – you might call those minor ● those kinds of changes that could be made with notification but not prior approval, and ● the kinds of changes that should be made only after the owner reviews and approves the changes.

You should really be thinking about the risks the type of change that is contemplated would present to the product quality. That is your driver. You should discuss, agree upon, and document procedures for conducting validation activities that would be required to implement any of those changes.

**Expectations on Inspection**

To turn a little bit to what I think you are all also probably interested in: what to expect when we are inspecting. There are no new rules at play here. This is a draft guidance. And as I said very early on, quality agreements are not explicitly required for regulations. We are going to continue to inspect against the act and CGMP regulations as they apply. Everyone is still subject to the same requirements that they were subject to prior to the draft guidance. But what is new, hopefully, is some clarity about our expectations. And again, this is still in draft, so the final guidance can really tell you how it comes out.

Some clarity about our expectations when we routinely request and review whether you have a quality agreement in place or whether you do not: The implication, I think, from the draft guidance, is that it would be difficult – it is possible if you can show us – but it would be difficult to engage in a compliant contract drug manufacturing operation without having a written quality agreement in place. So that does not mean, full stop, that you must have one. But we think they are the best way to facilitate compliance with the requirements.

As with any inspection, there are some possible outcomes: ● warning and untitled letters ● regulatory meetings ● seizures ● injunctions ● sometimes PAI withholds, and ● [although] we cannot require them, you might find that it would be prudent to recall a product.

Something very important that I think you may not know we care about is whether there are reputational harms to your business or to whether or not patients will buy from you. If there is a problem with you, the contracted manufacturer, or you, the owner that is having a contract manufacturer make your drugs, that could certainly be a problem for you.

**Warning Letters**

So just some snippets of warning letters: I think these sort of showcase the things we are concerned about and that we have written up in warning letters.

- This is a case of a contract facility pointing fingers at the product owner. ‘You said you told your clients that they will not validate their methods.’ So the contract manufacturer will say to the agency, ‘oh, we told our clients this was important but they did not do it. So we are off the hook, right?’

No, you are not. This is where you might end up with a warning letter that indicates [the contract manufacturer] is responsible for ensuring that the test methods that you used are validated. And that is certainly the idea that you are responsible for complying with the CGMPs that apply to the kinds of manufacturing activities that you are engaged in. So if this is a contract test lab and they would say to their clients, ‘oh it is important to validate’, but the client might say ‘well we are not going to do it.’ It is not an excuse then for the contract lab not to.

- The importance of communication between the parties is underlying in several of these letters. This is a letter
to the contract facility. You need to indicate how you are going to tell your customers about the problems that you have found. And when you found problems, how did they relate not just to the specific product that a given customer had? Are you going to inform your customers about how other products are impacted? Once again, that is part of compliance and CGMPs anyways, right? You have to extend your investigation to related batches or other products that might be implicated, but it is also important for a contract facility to tell customers about things that might affect their products.

- We have had a more recent letter related to data integrity. This is an issue that is cropping up all over the place for the agency. We expect contracted facilities just as much as owners to be responsible for ensuring that the data that they generate and the test results are properly documented, maintained and reported. So they need to investigate, and they need to have the same kinds of controls over the integrity of their data that they would expect for a primary manufacturer.

- This was a warning letter a few years back – sort of a novel approach that we took. We found some problems at a contracted facility, and in addition to sending them the warning letter themselves, we also sent copies of the same warning letter to the CEOs of five of the contracted facility’s customers. So you know, maybe if you won’t tell your customers, we might tell them for you. That was a novel approach. I only know of one instance in which we have done that. But it is certainly a possibility in the future.

- So here is one to a product owner regarding the disposition decision – again underlining the idea that the product owner is responsible for evaluating the quality of the batches of drugs that are made by the CMO to make an appropriate disposition decision. It could be approval. It could be rejection. And again, it does not necessarily have to be every step of making the evaluation. But the final decision does need to be done, and you have to decide between the two parties how much oversight the owner needs to have over the specific and discrete activities. Again, the idea of accepting and relying on certificates of analysis without verifying the information contained in them.

- Here is another one about, sort of looking forward: We found some problems with a product owner and they told us that, instead of continuing to manufacture the product themselves, they were going to engage a third party to do some of the testing for them. We indicated in the warning letter that, in their response, we would like to see the name and address of the contract lab, as well as a copy of the quality agreement that they plan to execute with the contract lab.

- Certainly in warning letters we have underscored this point that comes straight out of Q10 of the product owner having ultimate responsibility for the quality of the products. I have seen this language in several different warning letters. ‘Regardless of who manufactures the agreements that are in place, you are required to ensure that these products meet pre-defined specifications prior to distribution and are manufactured in accordance with the act and its implementing regulations.”

- The same language there. Again, a quality agreement does not just get you off the hook – you are responsible for what makes it to the market.

- In some cases, we have sent warning letters to both the contract facility and to the product owner. These are just some details about the language that came up, the two separate letters that we sent – a tandem effort. [A contract test lab repeatedly reported passing results when failures were obtained. They also failed to report accurate results to the client.]

**Summary**

So just to wrap up: Even in a complex market with a very, very complex supply chain, everyone who touches the products is responsible for product quality. Owners and contracted facilities should be working together proactively in the quality agreement to characterize and control the risks to product quality and patient safety.

A well-drafted quality agreement will promote communication between the parties and clearly delineate the parties’ responsibilities, especially with respect to quality issues. It is going to assure coverage of all the applicable cGMP requirements, and provide for change management. Finally, of course problems with quality agreements could have practical consequences for your patients and for your business.
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Successful Tech Transfer to a CMO Depends on a Strong Quality Agreement and Open Communication Pathways, FDA Asserts

A detailed description of how a drug product owner will transfer technical knowledge to a contract manufacturer needs to be part of a quality agreement, FDA officials are stressing.

They are cautioning that openness, in general, by the product owner regarding information learned in product/process development is needed for the transfer to be ultimately successful.

At the PDA/FDA conference in Washington in mid-September, CDER Office of Compliance Division of GMP Assessment Director David Doleski commented on the importance of the technical transfer process and the role the quality agreement plays in assuring its success.

“Quality agreements should indicate that owners of the application – NDAs, ANDAs, BLAs, and non-application products (OTC products) – have a methodology for transfer of the product and process development information from the owner to the contract manufacturer to assure a quality product will be manufactured in conformance with CGMPs,” he maintained.

“It is really important,” Doleski emphasized, “that we maximize the chances of success by transferring all available product and process development information to the contract manufacturer in order to have a successful launch of that product.”

Quality Agreements Help Bridge Company Cultures

A quality agreement can be an especially useful tool between companies that have “quite a lot” of differences in their facilities, equipment, procedures, quality systems, and knowledge and abilities of the personnel involved, Doleski noted. He cited the particular example of deviation management.

FDA recommends in its new draft guidance on “Quality Agreements for Contract Manufacturing Arrangements for Drugs” (see story on p. 12), released in May, that the agreement “should include a communication plan that explains how manufacturing deviations will be relayed from owners to the contracted facility and how such deviations will be investigated, documented, and resolved.”

Between two companies there may be a big difference in “the threshold for deviations, the timeliness of resolving those, and the individuals that are involved with resolution,” Doleski pointed out. To help mitigate those differences, “there should be a very good understanding that is reflected in the quality agreement about how that information is going to be shared back with the applicant – particularly with the technology transfer situation.”

He emphasized that the contract facility needs to be mindful that the product owner “has a broad range of experience in process and product development that can be brought to bear to resolve these deviations at a very early point in the technology transfer process.”

In addition to deviation thresholds and reporting, Doleski also cited sampling, testing, and method validation as areas that require attention in the quality agreement.

He has been noticing an uptrend in citations for methods that have not been qualified for use at the contract facility.

“I am not sure what is driving that,” he said. “But I think part of it could be inadequate provisions within the quality agreement. There is lack of understanding between the applicant and the contract manufacturer facility in terms of what the roles and responsibilities are.”

The draft guidance recommends that procedures for delineating controls over sampling and testing should be established in the quality agreement. Doleski commented that there should be “joint ownership over the transfer of methods with respect to qualification of those methods at the contract facility, and/or validation of those methods at the contract facility, if that is appropriate.”

Case Study Reveals Tech Transfer Pitfalls

At the PDA/FDA conference, Doleski provided a case study his office has tracked in which the lack of this joint ownership played out in a variety of GMP and tech transfer problems (Doleski’s full description of the case study and the lessons to be learned from it are provided below).

The case study is highly revealing on the pitfalls that can surface in contracting relationships.

In the case study, which was complicated by the threat of drug shortages, the product owner went through four successive contractors in search of a workable relationship.

At the end of his presentation of the case study, Doleski pointed to the lessons he hoped both product owners and contract manufacturers would learn from it:
Quality agreements are critical for contract manufacturing arrangements and should include how process development information should be transferred from the applicant to the manufacturing facility.

Product owners and contract manufacturers are jointly responsible for ensuring that the appropriate technical information is transferred.

Product owners should be forthcoming with the product knowledge and understanding they gained during development that may impact the manufacturing process, and

Process development information should be formally documented in writing and maintained in a document management system.

**FDA Role in Case Study Examined**

During the Q&A after Doleski’s presentation, participants at the meeting probed deeper into the case study he presented and the roles of the various participants.

One attendee focused on the recurrent nature of the tech transfer problems, and specifically on what role FDA played as the series of problems developed.

“I understand how this problem happened when going to a second manufacturer,” the questioner said, “but [then] it recurred at the third and fourth manufacturer. Do you think that the feedback that was given [by FDA] was really adequate? Was there anything the agency could have done to give more guidance to that kind of manufacturer?”

Doleski responded with an explanation of the agency involvement as the events unfolded.

“What we did in that situation was we came to realize that the applicant did not have adequate experience or understanding in order to address some of these problems. We started off with some telephone calls in order to apprise them on some possible approaches. Then we asked them for a formal meeting, based on one of the inspections.”

At the meeting with the product owner, the agency “gave them some guidance” on what it was looking for regarding development of the lyophilization process as well as on some of the “other issues” that had arisen.

The agency also “reached out to the contract manufacturers in terms of resolving the 483 issues, but also to talk about their relationship with the applicant to see if there was any advice that we could give in order to help facilitate a better relationship,” Doleski commented.

He emphasized that FDA was “very proactive,” particularly since the product was in a shortage situation. “We did reach out, as I said, several times to the applicant and to the contract manufacturers in order to give some advice. I think, as a result of that, that was some learning on the part of the applicant, although probably not as much as we thought they needed to bring the product successfully to market.”

Another participant asked Doleski for any additional insights he might have on why the sequence of events he described in the case study transpired.

“I think that part of the reason this happened is that there was a lack of appreciation for process development and tech transfer,” he commented. “I also think that the money was driving a lot of this. The choice of contract manufacturers was driven by cost considerations.”

Doleski stressed that the responsibility for a positive outcome lies primarily with the applicant. “I think that the applicant did not understand GMPs and did not understand process development. They were just looking for shortcuts in terms of getting this product to market.”

Also probed was the level of involvement of the quality units at the applicant and contracting firms.

Doleski commented that the quality assurance department at the applicant “was certainly not as involved as it should have been. I do not think that it was a very strong QA department. I think QA department at the contract manufacturer was much better. They were involved.”

However, he emphasized, the QA group at the contract manufacturer “should have been much more assertive up front in requesting that some of this process development information was provided to them. And they should have insisted on a much more robust level of information exchange than actually occurred.”
I have a case study that involves a company that has been having some difficulties over the past few years. The difficulties pertain specifically to process development and technology transfer.

This involved an approved product that was approved many years ago and is used in conjunction with a life-threatening condition. It is a lyophilized vial presentation. The manufacturer does not have their own manufacturing capability, so they relied on a contract manufacturer right from the very beginning.

**Second Contract Manufacturer**

This contract manufacturer performed some **limited process development**. Over the course of years, there were some GMP problems which ultimately led to the applicant deciding to terminate their relationship with this contract manufacturer.

So that is what they did. They identified a second contract manufacturer. They provided some batch records and procedures to the new contract manufacturer. That establishment proceeded to manufacture some lots and those lots were used to support the prior approval submission for transfer to that site. That triggered a pre-approval inspection.

The **pre-approval inspection** was performed and found that these were non-dedicated facilities used for filling and the lyophilization of the applicant's product and another product, which was a sensitizing antibiotic.

Unfortunately there was shared equipment for both products. There was cleaning that was performed between campaigns. However, no cleaning validation study was performed.

There were some deviations involved, because there was some spillage of the sensitizing agent, which affected the manufacturing area, specifically the filling area and the lyophilizer. That was identified and investigated, but testing revealed **presence of the sensitizing agent** on the equipment. So that presented real concerns with cross-contamination.

Additionally, the investigator found that there was a lack of development data for lyophilization cycle because the information had not been provided from the applicant.

Additionally there were some **high moisture levels** in the lyophilized product. Presumably because they did not have this process development data, they tried to transfer a lyophilization cycle from one site to another site, and that was not very successful, as you can see from the high moisture levels in the lyophilized product.

In response to the inspectional observations, the contract manufacturer agreed to initiate actions to decontaminate the facility. They underwent major renovations and they basically tore apart part of their facility, but in the process of doing that the relationship was ended between the applicant and the contract manufacturer facility.

**Third Contract Manufacturer**

So the applicant then pursued another contract manufacturer. They established this relationship was site number three.

This applicant provided batch records and manufacturing procedures to the contract manufacturer. There was not a lot of **process development information** that was shared with the contract manufacturer.

Basically there was the quality agreement, there were the batch records with procedures, but there was not a lot of insight and knowledge that was passed along to the contract manufacturer.

So the site did the best it could and produced lots in support of the supplement. These lots were used as part of the
submission for the prior-approval supplement for the site change.

The pre-approval inspection was performed. However, there were a number of inspectional observations. So because of a shortage of the product, the manufacturer went right on to manufacture lots intended for commercial distribution. However, they never performed process validation.

During the course of manufacturing a number of different lots, the lyophilization cycle parameters were changed. The reason that they were changed was because the initial lots were not successful in meeting product specifications. So there was a modification of the process.

This process, again, was based on batch records from the first manufacturer that had been manufacturing this for decades but had no supporting process qualification information. So they modified the cycle. Stability testing was performed. However, real-time stability testing at the second month revealed that there were failing stability test results.

Obviously there was a problem in that they could not manufacture the product and it was failing stability. Unfortunately, the applicant who was performing the testing did not share the results with the contract manufacturing facility. So the contract facility had no idea that this had failed stability, so they did not perform an investigation.

The contract facility was cited for their lack of investigation into stability failures, which you could argue is perhaps not completely fair since they were not aware of it. Nonetheless, they should have knowledge of problems with the manufacturing process.

The finished product specification for moisture was equal to or less than 10%. However, this was not scientifically justified. There was no data to support this specification. This is a rather high specification for lyophilized product moisture content. Obviously, this could have contributed to the problem considering the failing stability test results.

When they changed the cycle, there was no supporting stability data for the subsequent lots using the revised lyophilization cycle.

There were [some] issues with the calculation of target fill weights, which caused variability in the potency of the finished product. And during validation of the equipment sterilization cycle, operators deselected thermocouples if the values went outside the specified range. So, there were a variety of different GMP issues.

Fourth Contract Manufacturer

The applicant went on to find another new contract manufacturing facility. Truth is stranger than fiction – this actually happened. They went to a fourth contract manufacturer.

At this point, the applicant was starting to learn something about the process and what they should do for due diligence up front, so they performed a better assessment of the facility, equipment, and manufacturing capabilities.

They came to the joint decision that a new lyophilizer would be required. The contract manufacturer went through the qualification activities to qualify their new lyophilizer. Lots were manufactured in support of the supplement. The supplement was filed, and pre-approval inspection was triggered.

The problem was that because of the time constraints, and because of the need to get product onto the market, production lots were manufactured prior to the completion of the equipment qualification. They did things out of order.

Further, they found that there was a high range of temperature variation during mapping studies. So there were some issues with the control of the temperature from the equipment. That should have obviously been addressed prior to manufacturing lots.

Once again, there was a citation for the lack of process development for the lyophilization cycle. Basically, they transferred the batch record from the third manufacturer to the fourth manufacturer. But once again, they did not really
have any process development information.

The recurrent theme here is that there is not a very good understanding of the manufacturing process that is necessary to manufacture this product. So there was no temperature data for product vials during manufacturing of the lots. And of course, for lyophilization it is very important to know what temperatures the vials are experiencing during the lyophilization process in order to correlate that with the shelf temperature.

Visual inspection revealed a high incidence of meltback and collapse for product vials. Obviously there were problems with this lyophilization cycle, which resulted in a high number of rejected lots. So clearly they were not able to manufacture a quality product based on the manufacturing process that was given to them.

There were some additional GMP issues, [including] unknown peaks found in the finished product assay, which were disregarded by the contract manufacturer based on instructions from the applicant. There were issues with the media fills, aseptic technique, lack of environmental monitoring, and in-process specifications and in-process assay measurements to determine fill weight that were not supported by data.

Summary

So where am I going with this? Quality agreements are critical for contract manufacturing arrangements. Important elements should capture how process development information should be transferred from the applicant to the manufacturing facility.

If you are a contract manufacturer entering into one of these agreements, this is certainly something that you may wish to consider in terms ensuring that this process development information is transferred to you so that you can develop an adequate manufacturing process to manufacture a quality product.

Lack of process development information can lead to a situation where the product does not meet specifications. I think that was demonstrated several times over in this case study.

Process development information should be formally documented in writing, and maintained in a document management system. The initial situation here was that there was very limited process development information, and some of this was captured informally – it was never reduced to writing – and unfortunately the documentation was not available to the applicant. I think it is very important to maintain control over process development information.

Lack of formal process development information can result in lack of effective technology transfer to another location.

Finally, application approval can be adversely affected when inadequate process development and technology transfer is not performed.
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Level of Industry Response to FDA’s Quality Agreement Draft Guidance Reflects Contracting Challenges; Terminology at Issue

The raft of industry comments FDA has received on its draft guidance on “Quality Agreements for Contract Manufacturing Arrangements for Drugs” underscores the importance of having clear terminology when addressing the complexities in the contracting arena.

Given their depth and diversity, the comments will be challenging for the agency to assimilate – with various opinions expressed, in particular, on how the terminology issues should be worked out.

The comments do converge in supporting FDA’s emphasis on the need for a highly collaborative relationship between the parties, and suggestions are made on how to further emphasize these relationships.

The level of attention the draft guidance has received reflects the multidimensional challenges that companies have been wrestling with in their contracting relationships and the compliance breakdowns and product failures that have been occurring. (see story on p. XXX).

34 separate sets of comments were posted by FDA, received from 12 associations, 16 companies and six individuals. They range from a single paragraph to almost a dozen pages in length.

Associations submitting extensive comments included the Consumer Healthcare Products Association (CHPA), ISPE, and the Biotechnology Industry Organization (BIO). Briefer comments were submitted by PDA, Europe’s Active Pharmaceutical Ingredients Committee (APIC), and the Generic Pharmaceuticals Association (GPhA). Among companies submitting more extensive comments were Pfizer, McKesson, and a contract manufacturer that did not identify itself by name.

Along with terminology, areas receiving attention included: • the scope of the guidance • requirements around subcontracting • harmonization with ICH • responsibility for final product release • inclusion of the contractors’ procedures in a quality agreement and the need for owners to review them • communications and confidentiality concerns, and • laboratory facility requirements.

Definition of “Owner” Causing Confusion

ISPE requested that the agency “more clearly define the term as it relates to manufacturing,” noting that it “could be misinterpreted” as applying to a distributor of another firm’s products.

While acknowledging that the guidance is not intended to describe distribution relationships, the association suggested that the definition “clearly indicate” that the product owner is “usually” the holder of the NDA, ANDA or BLA for the product, unless it is an OTC product.

BIO similarly asked FDA to clarify that it “did not intend to sweep distributors into the definition of owners.” GPhA also requested clarification on the intended meaning.

Pfizer maintained in its comments that the terms “owner” and “product owner” are new and “may result in confusion regarding the holder of a regulatory filing or marketing authorization.”

It asserted that the definition “effectively establishes a new philosophy of holding accountable the last entity who has the product in their possession prior to introduction into the market for the entire supply chain.”

“As stated in the document and based on this definition,” Pfizer commented, “entities performing operations for the product owner are considered ‘contracted facilities,’ which conflicts with the current industry-accepted description of a contractor.” The company pointed out that there is no reference to the term “owner” in the GMPs.

CHPA also maintained that the terms “owner” and “contract facility” are “confusing,” advocating that FDA use the same terminology as ICH.

The OTC association recommended replacing “owner” with “contract giver,” and “contract facility” with “contract acceptor,” to be consistent with ICH Q7, Q10, and “common industry understanding and the needs of a complex supply chain.”

However, FDA compliance official Paula Katz explained at the PDA/FDA conference in September that the agency made a conscious choice not to use the ICH and EMA terminology of “contract giver” and “contract acceptor” since it implies that the relationship is based on the giver handing over the document to the acceptor (see story on p. XXX).

By contrast, FDA favored terminology that highlighted the importance of a long-term relationship in which each
party participates in drafting the quality agreement and understands the expectations for how the product or products are going to be made, what services are going to be provided, and how the quality units are going to work together to get that done.

From the agency’s point of view, an essential thrust of the guidance is that quality agreements – to be meaningful – should be drafted jointly by both parties and reflect the depth of understanding each has regarding their roles and responsibilities in the intimate relationship they share.

**Owner Definition is Main McKesson Concern**

CHPA pointed out that in its view the terminology as currently defined in the guidance “presumes that every holder of a product application is also a manufacturer.”

In a related point, the association stressed that the guidance “seems to be stating that the obligations for compliance with CGMP apply to the holder of an application, even if that application holder does not conduct any manufacturing activities.”

CHPA also noted that “product owner” is not defined in the guidance, and that it is not clear whether it is referring to “the holder of an application, the owner of the intellectual property rights for the product, or a company that books the sales for the product – such as a sole distributor who licensed such distribution rights from the application holder.”

McKesson also weighed in on the issue of the product owner potentially being misconstrued as an entity that does not perform manufacturing operations. Its four-pages of comments focused solely on the definition of “owner.”

Although FDA “likely did not intend to include distributors under the umbrella of ‘owner’ in the draft guidance, the definition of ‘owner’ is overly broad and, as written, will introduce significant confusion within the industry,” McKesson maintained.

The distributor pointed out that pharmaceutical distribution involves “a continuum of regulated roles” which may include: • manufacturer • repackager • private label distributor (PLD) • wholesale distributor, and • contract manufacturers of active pharmaceutical ingredients, finished drug products, biological products, and combination products.

“For this reason,” McKesson recommended that the final guidance make a distinction between the term “owner” and other existing definitions of regulated roles in the pharmaceutical supply chain. “Such a distinction will enable further clarification of the responsibilities of the contract manufacturer, repackager and PLD, as well as the wholesale distributor.”

**Should the Scope be Broadened?**

ISPE and BIO maintained in their comments that the scope of the guidance should be expanded – for example, to include development activities and groups other than the quality unit.

**BIO explained that while the guidance applies only to commercial manufacturing, quality agreements are “equally important during the development phase.”**

It commented that limiting the guidance to commercial manufacturing “may lead contract manufacturers to conclude that such agreements are unnecessary during drug development.”

The biotech association also pointed out that the guidance limits quality agreements only to quality unit functions. However, it maintained, “related operations are equally as important and should be included in the obligations and responsibilities of each party.” Also suggested was inclusion of intra-company agreements in the scope of the guidance, noting that such documents are usually reviewed by FDA during inspections.

**ISPE, in turn, recommended that the scope be expanded to include additional quality elements that it maintained represent “critical” aspects of an owner’s management oversight of a contract facility.**

The association suggested including a subsection for “exception-related events and outcomes” that indicates the level of involvement of the owner in a contractor’s decision to rework, reprocess, or re-inspect products, and in product acceptance.

**ISPE and BIO both advocated that responsibilities for shipping and storage of product should be in scope in the guidance.**

While BIO requested adding storage and distribution to the list of manufacturing operations contracted facilities perform, ISPE was more specific in what it recommended the guidance should cover.

The pharma engineering association commented that the
quality agreement “should allocate responsibilities between the
drthe parties for storing and transport of materials under
labeled conditions, including maintenance of required
storage and transport/shipping conditions until material
transfer from one party to the next,” and that responsibilities
for monitoring or validating shipping conditions should be
defined.

What About Subcontractors?

A significant aspect of contract manufacturing that the FDA
guidance does not address, and that as a consequence only
drew a few comments, is the use of subcontractors.

Noting this gap in the guidance coverage, the contract
manufacturer that submitted extensive comments pointed
out that subcontracting arrangements are common.

The guidance is written to address an owner and a contracted
facility, it noted, and does not address three-way party
involvement in manufacturing or supporting activities – for
example, the use of subcontractors by the contracted facility.
The CMO requested that the agency clarify its views on
subcontractors and its expectation on what kinds of controls
should be included in the quality agreement covering them.

Although there is a section in the guidance titled
“Change Control, Including Subcontractors,” the
two-paragraph section does not actually mention
subcontractors, both ISPE and Pfizer pointed out. A
search of the guidance shows that the term does not
appear anywhere else in the guidance other than in
the table of contents.

ISPE suggested that the guidance be revised using “strong
wording” to require a contracted facility to obtain approval
from the owner to subcontract any responsibilities that it
was originally contracted to perform.

It further suggested “that verbiage is included to cover
the requirements and expectations pertaining to the
subcontractor of the contracted facility, including a quality
agreement.”

Pfizer recommended that “subcontracted operations or
activities” be included in the section on activities requiring
owner notification.

Harmonization with ICH Suggested

In addition to CHPA’s recommendation for FDA to use the
ICH terms “contract giver” and “acceptor,” Pfizer and GPhA
made suggestions on content harmonization with ICH and
Pfizer pointed out what it maintains is a statement in the
guidance that contradicts ICH regarding starting materials.

Pfizer pointed out that the ICH Q7 Implementation Working
Group (IWG) is preparing a Q&A that “will address much
of the same concerns as outlined in this guidance” – for
example, regarding expectations for contract manufacturing
quality units. The pharma firm suggested that FDA hold
release of the final version of its guidance until after the
Q&A is completed “to assure alignment and minimize
confusion.”

Pfizer also maintained that the statement in the guidance
that “all contracted facilities must assure compliance with
applicable Current Good Manufacturing Practices for
all manufacturing, testing or other support operations
performed to make a drug(s) for the owner” contradicts ICH
Q7 and Q11 regarding the application of GMPs to the steps
of a synthesis prior to the starting material. It suggested that
the statement be revised to specify that it is applicable to “all
manufacturing steps performed within section S.2.2 of the
CTD.”

GPhA requested clarification on batch numbering
information, pointing to a phrase used in the
FDA guidance that references “batch numbering
processes.”

The association noted that contract manufacturers “may be
reluctant to provide this significant level of detail in a quality
agreement.” To meet the spirit of the recommendation,
GPhA suggested that wording be used similar to that in
ICH Q7 – that the owner is required to ensure the use of “a
unique batch or identification number.”

Can Final Product Release be Delegated?

Language in the draft guidance indicating that the final
release of a drug product cannot be delegated to a contract
manufacturer, ISPE and CHPA maintained, is contrary to
current industry practice and creates new GMP obligations.

The guidance states that “although the quality unit of each
contracted facility is responsible for release of the product of
the operations it performs, final product release of finished
goods for distribution must be carried out by the owner and
cannot be delegated to a contracted facility under the CGMP
regulations or any terms of the quality agreement.” It cites 21
CFR 211.22(a), “responsibilities of the quality control unit,”
which does not directly address the delegation aspect.

IPSE requested that the statement be deleted. “We agree
that the ultimate/final responsibility remains with the
sponsor. This sentence, however, adds a new requirement
to the cited GMP regulation. In addition, depending on the
circumstances (e.g., a “virtual” company), the sponsor may
not have the requisite technical knowledge for final release
(relying instead on expertise of a contracted facility for this
knowledge). In these cases, this new requirement would not be feasible or valuable.”

CHPA concurred with the ISPE position, emphasizing that “the statement that ‘owners’ are responsible for performing the release of products seems to create a new CGMP obligation for owners.”

The OTC manufacturers association maintained that “while it is completely agreed that an ‘owner’ is prohibited from introducing an adulterated product into market, the task of release could be, and in many cases is, delegated.”

It asserts that the draft guidance represents “a major change to how business is currently conducted” and “could have a significant economic impact within the industry, particularly upon smaller businesses that may not have the expertise or resources to review batch records and to perform other work necessary to release product.”

**SOP Inclusion and Review at Issue**

Four associations commenting on the guidance suggested that inclusion of contractor SOPs and their review and approval by the owner firm should not be part of a quality agreement.

PDA recommended against requiring specific procedures to be included in the quality agreement “since such an approach might inhibit the effective functioning of either party’s quality system with respect to continual improvement.”

CHPA commented that the guidance implies that all of the information related to the manufacture of the product should be contained within the quality agreement. “It is agreed that this information must be provided,” the association said, suggesting that the language be modified such that the quality agreement would define how the information is shared.

**Review and approval of a contract facility’s SOPs by the owner as suggested in the guidance also received industry pushback.**

APIC maintained that SOPs “are not usually relevant to specific products and are therefore not part of the usual documentation contract givers need to review and approve, as they are not part of the contract receiver’s quality management system.”

GPhA also stated that review and approval of contracted facility SOPs by product owners should not be a requirement, “as these SOPs may be common to other products, and often are owned by a separate party.” However, it agreed that any SOP uniquely required for a specific product should be reviewed and approved by the owner.

PDA extended the discussion to cover elements of the contractor’s quality system.

“In some instances,” PDA noted, “the guidance appears to be asking that the quality agreement include listings of parts of the CMO’s quality system. We recommend clarifying that the intent is for the quality agreement to assign responsibilities to parties by general categories rather than a restatement of individual GMP elements.”

**What Should be Communicated and How?**

How owners and contracted facilities will communicate with each other – especially regarding GMP deviations or the potential for cross-contamination and how responsibilities in those situations will be shared – also drew comment.

Pfizer suggested that the statement in the guidance that “the quality agreement should also indicate how the parties will communicate information about preventing cross-contamination and maintaining traceability when a contracted facility processes or tests drugs for multiple product owners” is too prescriptive, “as it requires the means of communication to be included in the quality agreement.”

ISPE, on the other hand, supported the statement in the guidance, commenting that it should be broadened to include notification to the owner when cross-contamination prevention measures are discovered to be inadequate.

The association suggested adding the following sentence: “In the event that the prevention measures outlined in the quality agreement are found to be ineffective, the contracted facility must notify the owner of any potential cross-contamination due to the production of certain products, e.g. hormones or cytotoxics.”

It further supported the communication statement by noting that while quality agreements “typically prohibit, restrict, or otherwise address the handling of hormones, cytotoxics, and other potent ingredients, they often do not include provisions on how parties will communicate the information.”

CHPA interpreted the language in the guidance regarding communications as requiring the establishment of a formal communication plan.

The OTC association noted that quality agreements should assign responsibilities for each party to notify the other party of various events and to identify contact persons for key quality topics. However, the term “communication plan” – used several times in the document – “implies the need for a new formal CGMP document,” CHPA maintained.
“If owners are subject to the regulations covering CGMP, and if a communication plan is a new CGMP document, then owners can be cited in a Form 483 for not having a communication plan or for having an inadequate communication plan,” it stressed.

BIO and CHPA weighed in on the how confidentiality concerns will impact what can be communicated – particularly regarding other products in a contract facility.

CHPA emphasized that, while the guidance’s expectation that a contract facility notify a product owner of changes, “including but not limited to…additional products brought into the line, train, or facility seems simple and important,” it is not always achievable “due to the contractual obligation of the contracted facility to maintain the confidentiality of the business information of its other customers.”

Notification by “class of compound” rather than referencing a specific product would be sufficient, CHPA maintained, and BIO concurred.

Who Needs Labs?

CHPA commented that the guidance seems to indicate that an owner is required to have lab facilities. The association cites the phrase “each participating party” as indicating that both the owner and the contracted facility “will have equally capable, redundant laboratory facilities and will conduct redundant testing and approval.”

Compliance with this language, CHPA maintained, “would require a major change in the industry,” noting that in many cases the very reason for contracting with an external laboratory is to access capabilities a company may not have internally.

BIO commented that in addition to GMPs, some contract manufacturing of drugs may also be subject to good laboratory practices (GLPs). While the draft guidance is “appropriately focused on GMPs,” BIO asked that GLPs be referenced as well.

DOWNLOADS FROM THE STORY:
FDA quality agreement draft guidance
Comments on the draft guidance from:
• BIO
• CHPA
• Unnamed contract manufacturer
• GPhA
• GSK
• ISPE
• PDA
• Pfizer
WORKSHOP: 11/19 - CONFERENCE & EXPO: NOVEMBER 20 – 21
BEIJING INTERNATIONAL CONVENTION CENTER

WORKSHOP: IPEC Regulatory Considerations (3 sessions)
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| IPEC 检测分析报告指南和IPEC重大变更指南 | Mr. Colin Li,  
|                                                | Mr. Martin Tao (IPEC China)                                             |
| IPEC Excipient Information Package Guide       | Ms. Priscilla Zawislak (IPEC Americas),  
| IPEC辅料信息文件(EIP)指南 | Ms. Meredith Ge (IPEC China)                                           |
| Hot topics discussion: Excipient Import inspection; Excipient Registration; Injectable Excipients related requirement. | Mr. Daniel Liu;  
| 专题讨论：辅料进口检验；辅料注册；注射用辅料相关要求 | Mr. Martin Tao;  
|                                                | Ms. Julia Zhu;  
|                                                | Ms. Nicol Feng;  
|                                                | Ms. Jenny Feng. (IPEC China)                                           |

DAY 1 - Wednesday, Nov. 20th
- Key-Note Speaker
- Educational Sessions
- Pharma Expo
- Poster Sessions
- Lunch
- ExcipientFest Cocktail

DAY 2 - Thursday, Nov. 21st
- Educational Sessions
- Pharma Expo
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INTERNATIONAL

Vetting of ICH Q3D Pre-Step 2 Impacts Final Draft; LVP and E&L Issues Could Warrant Further Public Comment

Large volume parenterals (LVPs) and extractables and leachables (E&Ls) from container closure systems were two issues on which the ICH Q3D Expert Working Group (EWG) requested input from stakeholders during the Step 2 drafting process without getting much feedback, and may warrant attention during the draft’s public comment phase that runs through December, EWG members are advising.

In general, the request that the EWG made for outside input (see IPQ “Monthly Update” December 2012, pp. 27-41) generated a plethora of comments that were used by the working group in refining earlier drafts. Safety assessments and assessing and controlling risk were among the issues on which input was sought that drew a significant response from those canvassed.

The number of comments that came in substantiated the EWG’s decision to do more extensive vetting than usual before releasing a Step 2 draft for public comment in the three ICH regions in view of the controversial issues involved and the wide-ranging relevance of the guideline across product types, lifecycle phases, and ingredient supply chains.

NSF Health Sciences VP Janeen Skutnik-Wilkinson, who has played a key role with the EWG in the Q3D development process, commented at a PDA Pharmacopeial Interest Group session, held in conjunction with the PDA/FDA annual conference in mid-September in Washington, that the lack of comments regarding LVPs and E&Ls was concerning.

“After many years of working with ICH, when groups are silent, I get nervous” she commented. “They are either not reading it or do not know how to go through the process of providing feedback.” She encouraged industry to take a look at the LVP and E&L sections in particular during the public comment process and provide feedback to the EWG.

Complicating the E&L assessments across different product types is that extractable information may be able to be obtained from suppliers while that on leachables tends to be product-specific. The relationship to packaging providers in making assessments is also at issue.

Two Pre-Step 2 Vettings for Q3D

Reflecting the concerns of the international regulatory community regarding elemental impurities and the desirability of a harmonized approach to the criteria and methodologies needed to control them (see IPQ Special Report Nov/Dec. 2008, pp. 37-39), the ICH Steering Committee set up a Q3D expert working group that produced a concept paper in 2009 (see IPQ Special Report May 2010, pp. 5-6). The concept paper served as the basis for the current draft.

Although modeled after the EMA catalyst guideline, Q3D addresses all sources of metal in a drug product rather than focusing primarily on those arising from the use of catalysts. The ICH guideline calls for the various potential sources to be covered in the risk assessment and control strategy risk mitigation.

The EWG began drafting Q3D at the meeting in Tallinn, Estonia in June 2010 and had produced a draft by the ICH meeting in Seville, Spain in November 2011 that it felt was close to Step 2 form.

However, given its broad applicability across different product types and the complicating toxicological and technological issues raised, the group decided to break from ICH tradition and air a pre-Step 2 draft through its constituent organizations in late 2011 to make sure that the approach it was taking represented a broad consensus and that outstanding concerns were identified and addressed. The result was a plethora of comments, leading the EWG to decide that another pre-Step 2 airing was needed.

In December 2012, the EWG vetted a second, pre-Step 2 draft to draw further input, with the target of achieving a draft that would meet the Step 2 ICH consensus criteria by mid-2013 (see IPQ “Monthly Update” December 2012, pp. 27-41). The draft was finalized at the June 2013 meeting in Brussels, Belgium, clearing it for public comment.

At the PDA Pharmacopeial Interest group session, Skutnik-Wilkinson explained that the EWG had anticipated that the
At a USP Science and Standards Symposium in Baltimore, Maryland in mid-September, AbbVie NCE Analytical R&D Director Mark Schweitzer, who served as the EWG rapporteur, commented on the time spent producing the Q3D drafts.

“A lot” of the work done on ICH documents, he explained, is done in face-to-face meetings, “but those meetings are only active once every six months.” By contrast, his EWG “met twice weekly for periods of six months at a time during this period covering about two years to keep the progress moving forward.” [Editor’s Note: See box above for a Q3D timeline provided at the USP meeting by Schweitzer.]

The added face time provided the EWG and constituent company members more opportunity to have “significant” discussions. Noting that it took a little over three years from concept paper to a Step 2b draft, he emphasized that “for those of you who have experienced ICH processes, this was not too slow.” ICH’s EWG on M7 (Mutagenic Impurities), he noted, “beat us in the total time from start to Step 2 by about six months.”

The Step 2b draft is a lengthy 79 pages, the bulk of which (45 pages) comprises an appendix on individual safety assessments - including the known toxicity data and parenteral, oral and inhalation PDEs for each of the two dozen elemental impurities specifically addressed in the guideline.

The main body of the document is 14 pages, and includes detailed sections on elemental impurity: ● safety assessment ● classification, and ● assessment and control. Short sections address speciation, analytical procedures, lifecycle control strategy management, and submission recommendations.

Along with the appendix on individual safety assessments, rounding out the document are reference and glossary sections, and three additional appendices covering: ● a method for establishing exposure limits ● generally established PDEs for elemental impurities, and ● an example illustrating calculation options for converting PDEs to concentrations.

**Excipients in Scope But Limits Do Not Apply**

A key point regarding Q3D, Skutnik-Wilkinson explained in September, is that for the first time in an ICH document excipients are within scope, which she characterized as both “great” and “complicated.”

Formerly with Pfizer before joining NSF/DBA in October 2012, and past chair of the International Pharmaceutical Excipients Council (IPEC), Skutnik-Wilkinson has represented PhRMA and then IPEC in the EWG deliberations on Q3D. [Editor’s Note: For Skutnik-Wilkinson’s complete remarks at the PDA interest group session, see box below.]

Excipients are in scope because they contribute to the total elemental impurity load in the product in which they are used. However, the limits in Q3D apply to the finished product, not to individual excipients - which has been a source of confusion.

“One key message, and a key principle that we put into the guideline is that we, as pharmaceutical manufacturers, cannot and should not insist that the raw material suppliers meet extremely low specifications or eliminate metals,” Skutnik-Wilkinson emphasized.

She noted that some drug companies have contacted excipient suppliers and asked them to meet the Q3D limits in their materials, which “is the wrong message, and it would
Advice From Skutnik-Wilkinson
On Mined Excipients

During the Q&A after her presentation at the PDA meeting, Skutnik-Wilkinson responded to a question regarding the variability of elemental impurities in mined excipients and how to approach calculating their contribution in the final product.

The PDEs are set based on the dosage form. So as a company, what I suggest, and what I suggested to my prior company before I left, is to look at all the formulations with mined excipients. Then look at how much the mined excipient is a contributing factor. Take out the worst cases. Then look at if you get, say, 10ppm of lead or mercury, what that is going to do the overall contribution. You can try to work that out.

There is a calculator tool that IPEC developed that is available for free so that you can look at how that will affect the PDE. You could then work with the supplier and let them know that you have X number of products, what the worst case is, and that you would like to put in a requirement that, if possible, you not receive material above a certain level. It still could be very difficult. It really depends on what the material is....

The best thing is to engage in real discussions with the suppliers. I would suggest the quality or technical people rather than the procurement person. [For more on the mined excipient issue and the PDA calculator, see the story on p. 40].

Safety Assessments Draw Comment

In response to the stakeholder feedback, changes were made to the Q3D draft regarding safety assessments for various routes of administration – a point where EWG and pharmacopeial opinions have differed.

The EWG, Skutnik-Wilkinson said, performed an “extensive review of all the public literature” on toxicity of the various metals and the permitted daily exposures (PDEs) that have been established for most metals by route of administration to address the comments.

During his presentation at the USP forum in Baltimore, Q3D rapporteur Schweitzer emphasized that the tox assessments performed by the EWG were “as extensive as I have seen in the industry.”

The group sought out and reviewed original papers, including “some obscure papers that we could only find in the archives in a University in Seattle” to get the data to support the quality of the safety assessments, he explained.

The elements targeted were based on constituent feedback, and included assessments “for some elements that are not commonly used, but people wanted to see limits established for.”

Notably absent in the Q3D draft are the related PDE levels for all of the common routes of administration for the impurities listed.

At issue is the lack of toxicity data for some dosage forms – for example, parenteral, inhaled and topical routes – and differing opinions on how or whether to extrapolate the data that is available.

Skutnik-Winkinson characterized the route of administration omissions as “a major issue and diversion between what the regulators and industry and the EWG say, and what the pharmacopeias say. This is something that really deserves more comment, particularly back to USP, in terms of the industry view.”

At this time, USP advises using the PDE that applies to an oral route for other routes of administration for which the toxicity is not specified. However, Skutnik-Wilkinson emphasized that the EWG “felt strongly” that it should not “arbitrarily assign PDEs just because they exist for other dosage forms.”

During a Q&A session after his USP presentation, Schweitzer addressed the question of controlling elemental impurities in dosage forms for which there was no good PDE data – for example, topical administration.

Noting that toxicity data for the impurities in dosage forms other than oral is “extremely low,” he said that the EWG’s recommendation for indications other than oral, parenteral, or inhalation is to refer to the PDE for the parenteral route “and do a risk assessment and an assessment of what you need to control for that drug product.”

What If There is No Data?

Additional guidance was included in the Step 2b draft in response to comments on risk assessment and risk control – in particular, addressing situations where toxicity data for
ICH Q3D RAPPORTEUR MARK SCHWEITZER ON THE ESSENTIALS OF Q3D

In his presentation at the USP symposium in mid-September in Baltimore, AbbVie NCE Analytical R&D Director Mark Schweitzer, who served as the EWG rapporteur, highlighted key points in the guideline, and the processes, thought patterns and stakeholder feedback that impacted it.

Q3D as it stands now is modeled closely after Q3C on residual solvents. A lot of the elements are there. The risk assessment approach and the safety approach use the same approach that is used in Q3C.

We had a very high-level approach – a standard rubric – where we looked at the available information on toxicity of each of the elemental impurities and came up with the permitted daily exposures [PDEs]. We started out with the EMA guideline on catalysis and metal reagents. We looked at USP <232>.

The safety assessment factors that we considered were the oxidation state of the metal most likely to be present in the drug product. In some cases, that may not be the most toxic species – for example, chromium VI in the inhalation mode is a known carcinogen. However, in most drug products, chromium VI is not going to last and is not used in most chemical processes. The most likely species seen is chromium III. However, its speciation will help you build your safety assessment and risk assessment would be of benefit in putting your application together….

In our reviews with our constituents we looked at their feedback and went from 14 elements in the EMA guideline to 38 that we assessed during this process. In Step 2, you will see that that is paired down to about 24 elements with established PDEs. We have included reference to ten additional elements based on constituent feedback.

In the absence of information, people were concerned that if we did not say anything about certain elements that they would need to test for them. For those that we actually did the safety assessments which found them to be essentially non-toxic or controlled by other GMP methods, we have those listed in the guideline for reference. We say, ‘if it is one of these ten, unless you know that there is a specific toxicity in your drug product, you can ignore them for the purpose of risk assessment and control of elemental impurities in your drug product….’

Potential sources of elemental impurities are discussed in the guideline. It is very basic. We wanted to provide guidance to say, ‘in a risk assessment, consider everything.’ Some things may have a low risk because of a low probability of inclusion of an elemental impurity from that component. But this is the spectrum of what you should consider – do not necessarily test every one of these – but consider them in the risk assessment.

Once you look at each one of those, then they need to broken into potential sources of metal impurities – for example, from the API. Do you have an intentionally added element or metal? Is there a contribution from the manufacturing equipment or the nature of the environment or from the container closure system? Make those evaluations and understand where the sources are and come up with a control strategy.

In doing that you essentially look through a number of alternatives and a number of approaches where you have potential elemental impurities carried through to the drug product…and determine where you need to apply other controls.

A table that we included in Step 2b tries to answer the question, ‘do I have to test for everything in every product?’ We tried to be very explicit. For the elements that you intentionally add, yes, you will need to have some data on them for the drug product. Data in this case means some analysis, somewhere in the process.

But if they are not intentionally added, then there are a number of categories [they may fall in] because of low prevalence or low natural abundance or low probability. You do not necessarily have to consider them during the assessment – for example, thallium. A lot of people have asked me about why we included thallium in the guideline. The EWG included thallium because a number of constituents asked about what the limit of thallium would be if it is in the drug product. We tried to be responsive to the entire constituent group.

Once you have identified that, control elements can be established for the incoming material controls, in-process controls, quality system controls, and process equipment and component design to ensure that in the final drug product you have either controlled it through all of the upstream factors, and GMP controls as well, or you have to
Additional controls, he noted, can come through testing or additional steps in the control strategy, with the goal of ensuring that the levels of elemental impurities in the drug product are below the PDE. The guideline walks through a four-step process designed to: identify, analyze, evaluate, and control elemental impurities in the drug product. After identifying the sources of potential elemental impurities, the data needs a thorough analysis. Schweitzer explained that the data can be sourced from a variety of places, including the available literature and existing knowledge in the firm performing it.

“In my company,” he noted, “during development we routinely run ICP [inductively coupled plasma] screens to look for a number of different elements and metals that we are pretty confident are not there.” He explained that while developing a broad range of chemical syntheses for its APIs over the past ten years, his firm has built up an evaluation database. “So we can state that our reactors are not dissolving, and [we have] the data to prove it. So from now on we will not be monitoring for chromium, vanadium, or molybdenum” that could be contributed from stainless steel reactors because we have established that over a broad range, our processes do not contribute them.”

The final step is looking at the data and knowledge “to determine what elements you need to control in the final product. That control needs to be communicated in the regulatory filing.”

Focus on Safety by Controlling Impurities

Schweitzer explained in his USP symposium presentation that two key themes emphasized in the Q3D draft are: a safety focus based on the toxicity of the elemental impurities, and a risk assessment approach to understand which elements are controlled by the design of the process and which need to have additional controls. Additional controls, he noted, can come through testing or additional steps in the control strategy, with the goal of ensuring that the levels of elemental impurities in the drug product are below the PDE. The guideline walks through a four-step process designed to: identify, analyze, evaluate, and control elemental impurities in the drug product. After identifying the sources of potential elemental impurities, the data needs a thorough analysis. Schweitzer explained that the data can be sourced from a variety of places, including the available literature and existing knowledge in the firm performing it.

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The final step is looking at the data and knowledge “to determine what elements you need to control in the final product. That control needs to be communicated in the regulatory filing.”

Downloads from the Story:

- ICH Q3D Step 2b draft
NSF HEALTH SCIENCES JANEEN SKUTNIK-WILKINSON ON ICH Q3D STEP 2B DRAFT

During her presentation addressing a Pharmacopeial Interest Group at the PDA/FDA annual meeting in mid-September in Washington, D.C., NSF Health Sciences VP Janeen Skutnik-Wilkinson provided insights on the development and finalization of the ICH Q3D Step 2b draft based on her service on the Expert Working Group (EWG). Her remarks encompassed: ● the history of Q3D ● complexities of the issues involved ● key principles ● the revision process, and ● pharmacopeial impact.

I have spent a lot of my life prior to joining NSF Health Sciences working with [session moderator Sue Schneipp] on various pharmacopeial topics. I also worked on running and starting-up compendial programs at two companies – Merck and Pfizer. I do not have as many years experience as Sue, but I spent a lot of my career navigating through pharmacopeial waters. For my sins I have also spent a lot of my career navigating through ICH. If anyone thinks that dealing with the pharmacopeias is a difficult task, I will just tell you that is easy in comparison to working in ICH.

I am going to give you an update of what is going on with Q3D, where we are, and impacts from a pharmacopeial perspective....

**Q3D History**

So why do we have Q3D? I guess in my naivety, my ignorance, my belief in strong science, myself and a colleague from Merck thought, ‘heavy metals – we have been talking about that for years.’ I was at an AAPS podium in 2002 talking about challenges with the heavy metals test that had been in existence for over a hundred years and nothing had been happening. We were talking about it in 2002, ten years went by and nothing was changing... There were no harmonized guidances globally – in ICH or any other regions – and essentially we were trying to establish appropriate controls. We were really concerned..... If anyone was following the work that the PDG was doing with regards to harmonization, heavy metals had been on their agenda and then it dropped off.

It dropped off because we had Europe developing metal catalyst guidelines; we had USP going their own direction; and Japan was kind of caught in the middle and was uncomfortable – and rightly so. Despite the fact that it was on their agenda, everybody was going off in their own direction. So I and my colleague at Merck...thought ‘hey, we need to get together, we need to have a harmonized solution for this.’ We cannot possibly as an industry deal with multiple different standards for metals.

So we put together an ICH concept paper and a business plan, and got Q3D added to the ICH agenda. You think I would know better because I was on another ICH topic, but I thought this would be easy because we had the metal catalyst guideline and we had established practices and viewpoints from almost one hundred years of where we need to go. I thought it would only be a few years. But now it is 2013 and we are still making progress.

As I said, if anyone heard my previous talk, anytime you have to deal with public standards in multiple regions around the world...you can think about the exponential amount of time it takes to achieve a public standard.

**Complexities of the Issues Involved**

The complexities of Q3D really did not come to light until we started to delve into it. The more discussions we had, the more the team realized that it would be more complicated than residual solvents due to the fact that metals are inherently present in the environment. We are not talking about situations where you just add a catalyst. The majority of problems, from an excipient perspective, come from these materials that are mined or sourced from the environment, like talc and carrageenan. There was a report last week that carrageenan and other materials that are derived from the sea are becoming much more attractive for companies to use in pharmaceutical formulations.

You have arsenic and you can have mercury in various materials you pull from the sea. A lot of our excipients are mined, and so of course you can have various heavy metals, like lead – it is in the ground, it is going to be in the ground, you cannot get rid of it and you cannot process it out of these materials. You dig them out of the ground, you purify them, and the lead is still there. So that became a huge complication and discussion that we had to go through as part of the process.

One of the things we wanted to do in developing the guideline, and also in the aspects that come into play from a
pharmacopeial perspective, was to make sure that it was comprehensive – make sure that if there was a concern from the regulators, from the public health perspective, with metals, that we were not only going to deal with metal catalysts, because that is easy. Then there is really no point in having a guidance.

The process – and we were fairly adamant when we developed the actual EWG, or expert working group – was to have a balance of quality and toxicology folks, because we felt we could not arrive at a reasonable guideline if we only had toxicology folks or quality folks in the room. We needed the toxicologists to tell us, ‘here is all the safety data that exists for all of these metals and what the patient risk is,’ and we also needed the quality folks to get an understanding of what is realistic and what is really there.

We cannot possibly have a limit of zero, because then we would have no drugs. It would be impossible. Because unfortunately, again, a lot of excipients come from the ground, and naturally have lead in them, and there is not a whole lot you can do about it. It is not a case of reformulating, because there aren’t alternatives to those materials. So it was really important to have those two groups working together to develop the guideline.

The guideline does contain detailed safety and toxicological assessments that have been done for each of the metals. I am on the quality side. I am a chemist. I am not a toxicologist. But the amount of time and effort that has gone into these assessments by the toxicology counterparts is impressive. For anyone who has seen the guideline, the bulk of it is the toxicology assessments. We felt it was important to include all the specifics, so that your own company toxicologists can understand how the information was arrived at and what was used in terms of studies.

We wanted to make sure that we really used what is appropriate and that that information is transparent, so that anyone, be it a regulator or a company, has that information.

We did use the EU metal catalyst guideline as a guide. As you guys know, that was really focused on the same type of approach as residual solvents – so whatever you basically use is what you would then limit. One important deviation, perhaps, from the typical ICH process, is that excipients are within scope. This is really the first ICH guideline that puts excipients in the scope, which is great and also complicated.

The reason for that is that now what you have is companies running around like crazy sending questionnaires to all of their suppliers. I have seen some of them, and they demonstrate a lack of understanding of the guideline because they request excipient companies to comply with the ICH limits. The ICH limits apply to the finished dosage form. The limits in Q3D do not apply to the excipients. Excipients are in scope because you have to take their contribution into consideration. Obviously, if you are looking at a simple solid oral dosage form – one API and four excipients – you have to know how those individual excipients contribute to your overall metal load so that you can determine if your product actually meets or is below the total limits for each of those metals.

There is still an awful lot of confusion with regard to how that guideline is going to be applied. However, we still have a lot of time to fix it, because we only just reached step two, which I will talk about in a minute.

**Key Principles**

So what are the key principles? Risk, risk, risk, risk, risk. And the reason why I want to drum home the risk message is that there is a misconception. There is also a misconception with the use of the USP chapters – that you have to go and test everything for all eternity – every lot, every excipient. And we have had this discussion within the EWG. If our intent was that you would test everything, we would not need a guideline. All we would need is maybe a paragraph that says, ‘here are all the levels, test everything, make sure it meets it, done.’ That would have been the easiest ICH topic ever. We would have been done in one day.

But that is not the point. The point is that you have to assess what the risk is from all of your materials, all of your components and your manufacturing equipment, and [decide] how you are going to manage that risk. How you manage that risk is not to call your supplier and say, ‘okay we know you have five parts per million of lead, get rid of that lead.’ It doesn’t work. It is figuring out that excipient X has five parts per million, it is inherent in the environment, nothing we can do about it, so what are all the other elements within my formulation, and how can I deal with it?
If you do get into a situation where you exceed the **PDE** [permitted daily exposure], the regulators have been extremely open and transparent, as have the pharmacopeias, to ‘come and tell us, come and tell us you have a problem.’ If there is something that you can do from a reformulation or from a processing perspective, they will ask for your plan for how to do it. If you cannot, have that discussion about how it is impossible to get it out of the process – that it is going to be in the product, that it is a medically necessary product – so how are we going to move forward?

We have members from Chinese Taipei on our EWG and we have folks from various parts of Europe. We have had regulators come in from various parts of Africa. WHO has been involved. They have said numerous times that they want you to come and talk to them if you encounter problems.

To date, in all the **data collection** we have done in the EWG and in partnership with FDA we have not yet found a problem where a product will not comply with the PDEs. That is not to say that there may not be one, but to date, in all the data collection we have done, we have not seen that.

Again, testing is not the default. So if there is only one thing that you take away…that is the key message. If you are a pharmaceutical manufacturer, get back to your procurement folks to make sure that they understand. And certainly if anybody runs into any issues, send me a message. I have done this already for numerous companies. I have gone and talked to their folks. We can send them bits of the actual document to help them understand what it is that the regulators are expecting.

Be very careful about the consideration of **possible sources of metals**. Just as you need to understand the GMP aspect of your materials, you really need to understand whether you are dealing with naturally-derived materials or synthetic materials, and what the risks are with those. You do not have to do it yourself, though. If you spend some time in that relationship with your supplier, most of them already know what the risks are, and most of them already know what is likely to be there. They may know for other reasons because of other industries that they serve. If they work with the electronics industry or the food industry, there are certain things that they need to be concerned about. Be very open in listening to what they have to tell you. They may not have a method that is validated to ICH standards. But they may have ten, fifteen, twenty, or fifty years of data that you can use as part of your risk assessment. So be a bit broader in terms of how you are thinking about collecting data.

One **key message**, and a key principle that we put into the guideline is that we, as pharmaceutical manufacturers, cannot and should not insist that the raw material suppliers meet extremely low specifications or eliminate metals. The actual levels in Q3D are for the finished product, not for the ingredients. So to send someone the guideline and say that every material they send you has to meet this – and there have been a few companies who have done that – is the wrong message, and it would be impossible to do that. It is basically taking your problem and throwing it down to your suppliers. When you think about most of the suppliers, they basically provide a very small amount to our industry. You can see how you are not going to get somewhere very quickly by doing that.

Cellulose is a great example. Most people in pharma that I have talked to in the last ten years will say, ‘we use so much cellulose, it is such a big component.’ We in pharmaceuticals use less than .02% of the total annual production of cellulose. So you have to look at it from the perspective of what makes sense and how we work together with our suppliers to achieve the right result.

**Guideline Revisions**

What are the revisions that we made in the guideline? We actually went through…three different internal consultations. That was within all the different organizations that are part of the EWG. We went through multiple iterations just internally. I think the first time we sent it out for consultation we got 1200 comments. And the reason for that was that we realized that this was really a game changer, a change of philosophy, a change in how we were looking at things, and that there were really a lot of unknowns out there.

If you look at the **existing tests in the USP**, they do not tell you that you have five parts per million of lead or two parts per billion of arsenic. There was really nowhere to get that data. So we knew we had this big unknown that we had to solve. Trying to get it out there so people could start digesting it and understanding it, and also making sure that the key messages, the key principles, were getting through [was important].
We revised all of the various safety assessments to take into consideration the comments that we received. All of that was verified. Then we did an extensive review of all the public literature that was out there on those various metals. PDEs have been established for most metals and routes of administration. You will notice in the guideline that certain routes of administration are absent. This is where there is a major issue and diversion between what the regulators and industry and the EWG say, and what the pharmacopeias say. This is something that really deserves more comment, particularly back to USP in terms of the industry view.

The toxicologist viewpoint, in terms of dosage form: For topical or dermal, there is no real, good toxicological data to tell people what the risks are of metal exposure for those types of dosage forms. So the toxicologists and the regulators said, ‘if there is no data, we cannot possibly establish PDEs, because that is random and it goes against the first principles we agreed to in the EWG, which are science and risk-based. We are not science-based if we set arbitrary limits.’ At the moment, the way the USP is written is to use the oral route. So there is still an issue there. When our EWG meets again next summer, we will be continuing to discuss this. The group felt strongly that we cannot arbitrarily assign PDEs just because they exist for other dosage forms.

We also provided metal classification to facilitate risk assessment. The big four [designation was] not initially part of the guideline, everyone started calling them that and saying that they treat them differently, whether it was industry or the regulators. So we said, ‘if we are going to treat them differently, shouldn’t the guideline address it that way to make it clear to folks that these are different because of their extreme toxicity?’

So the guideline has a subset of items that are extremely toxic. It does not exactly say, ’should be avoided.’ There is a reason for that. As I said before, a lot of those metals come from the environment. So there is a concern that if we say ‘should be avoided,’ we are going to get people saying to their API suppliers, to their packaging people, ‘whatever you do you have to come back with a level that is zero.’ I can tell you that there are companies out there who will provide you with material and tell you that the level is zero. I can also tell you that you probably never audited that facility. But I am not kidding. There are companies who will tell you they can do that and that whatever the spec is, they absolutely meet that. This is not really in line with what we heard this morning about quality culture – quality culture does not exist in those companies. You have to be very careful.

The control strategy section has been completely revised. We made a lot of changes to the content to add clarity and ease implementation. You guys can probably relate to this: With anything you know really well or have dealt with for a really long time, there is stuff you just know, you understand of course. It is what you deal with. Many of you with children have gone through those life lessons as a parent, where something completely obvious to you is not so obvious to your teenager. So that was part of the constituent review: There was so much that we discussed over all of these years that we automatically read into the guideline because we have been dealing with it for so long. When we sent it into the review, people were missing certain key points, and so a lot of that had to then be added into the control strategy.

Additional guidance was included for risk assessment and risk control. This is still an area of concern. Because if you have materials that you have no data on, and you cannot find a lot of data from the literature or from your suppliers, someone at some point in time is going to have to collect that data. So it is confusing to some people how to go ahead and do a risk-assessment with no testing. There are certain elements – some testing that someone is going to have to do to get that body of knowledge. Again, it is not going to be for all eternity. You are not going to be testing those materials for all of time. You are not going to be asking your supplier to do those tests all the time. So it is a little complicated. Hopefully the guideline as it is written now makes it a little bit clearer how you do those risk assessments and how you determine whether your product is at risk of failing the PDE.

We provided a lot of additional information with regards to the actual calculation options, and examples, really to help people understand how to walk through it.

So where are we? We signed Step 2 in June of 2013. The document is out for public consultation. It took a far more significant time than I would have thought to get published in the Federal Register and translated into Japanese. So it is out and I believe the final date of commenting is in December.
I have talked within PDA regarding how PDA is going to respond. I know PDA is going to put a team together to comment on the ICH guideline. I have volunteered to lead it because I know a lot about it. Certainly if you are interested, let someone from the PDA staff know you are interested and they will let you know how to get involved. I am there to lead it but not there to influence it. I am just there to get people together, and if questions come up I will be able to answer them because of my involvement.

**Pharmacopeial Impact**

Regarding the pharmacopeial impact: This has been a very difficult process, perhaps. There has been the public face of what has been going on and there has been a lot of behind the scenes stuff. USP had committed from day one that they would revise what they were doing when ICH came out, and they have held to that commitment. There were a lot of doubts about whether that would happen, and I think there was a lot of influence and push from FDA and industry to ensure that would happen.

I think everybody knows that USP has **postponed the implementation** of where they are going. They have set up a variety of project teams to discuss all the different ramifications, including the supplier and dosage form aspects. So if you are not actively monitoring the USP website, I encourage you do to that. There is a ‘hot topic’ on elemental impurities. It will tell you all the different project teams, where they are and what they are doing.

USP is open for feedback. So if you have specific issues that you want to raise, I think the more voices there are, the better, especially the voices that are not always the same voices. Sue [Schniepp] can attest to this. For many years on many topics, it was Sue and me talking about something, even though we were representing our constituents, we were representing pharma. But if you are the voice for ten years, then they look at it and say ‘it is just Sue and Janeen that have this issue.’ And we [responded], ‘no, we are actually commenting based on what 200 people told us.’ So it is also good for people and for companies who may not have traditionally reacted to stuff like this to put your voice in there and to be heard.

The EU is holding on their implementation of their revised metal catalyst guide. And Japan, in the fashion that we would expect from JP, is waiting for ICH. So they did not go off and develop anything in isolation. They are actually waiting for ICH to finish. Any implications with regard to the Japanese Pharmacopeia will come out after ICH.

We expect to sign **Step 4** in June of 2014. I cannot [be held to] that, because we have no idea how many comments we will get when we close in December. We could get another 1200. I hope not, because when you go through public consultation formally you have to address each and every comment officially. It is not like an internal review where you can go through them and generalize them. It is a laborious project. So how long it takes to triage them and how significant they are will then dictate when our deadline is going forward.
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IPEC and a Broader Coalition of Industry Associations Identify ICH Q3D Implementation Challenges and What is Needed to Meet Them

The International Pharmaceutical Excipients Council (IPEC) and the Coalition for Rational Implementation of the USP Elemental Impurities Requirements, of which IPEC is a member, have been taking a hard look at where the key challenges lie in implementing the elemental impurity standards in the new Step 2b draft of ICH Q3D and what tools they can provide to assist the pharmaceutical regulatory community in addressing them.

The goal of IPEC and the Coalition is to bring the pharmaceutical industry, its suppliers, the pharmacopeias and regulators together to collaborate and reach a common understanding of the implementation problems that need to be solved and where the most effective and efficient, science and risk-based solutions lie.

With ICH having reached agreement on harmonized elemental impurity limits, now emerging into high relief are the not insignificant issues around what further testing will actually need to be done to make the risk assessments that ICH Q3D calls for meaningful, who is going to do it, and how the results are going to be communicated and assessed for compliance through the regulatory chain.

Already emerging from the IPEC/Coalition pipeline are:

- an updated standardized information request form and cover letter that drug manufacturers can provide to their ingredient suppliers to better target and streamline the communication process regarding the ICH elemental impurity issues
- a risk-assessment tool for drug manufacturers to use in calculating permissible daily exposure (PDE) based on their specific formulation and daily dosing as they obtain information on potential ingredient elemental impurity levels, and
- a position paper providing data and information supporting the use of extractable/bio-accessible metal content vs. total dissolution/metal content, what can be learned from other industries on this score, and recommendations on how USP could move forward on the issue.

Coalition Supports USP/ICH Harmonization

The broad-based Coalition for Rational Implementation of the USP Elemental Impurities Requirements was formed several years ago as USP began development of its new Chapters <232> and <233> on elemental impurity limits and procedures, respectively. The two new chapters will replace the old USP chapter on heavy metals testing (<231>.

The goal of the group was to provide input to both USP and ICH on their respective standard-setting efforts and foster harmonization of the content and implementation timing (see IPQ “Monthly Update” December 2012, pp. 27-41).

Along with IPEC, the Coalition includes representation from: ● the Generic Pharmaceutical Association (GPhA) ● the Consumer Healthcare Products Association (CHPA) ● the Society of Chemical Manufacturers & Affiliates – Bulk Pharmaceutical Task Force (SOCMA- BPTF), and ● the New Jersey Pharmaceutical Quality Control Association (NJPQCA).

The Coalition, as well as its individual member organizations, submitted feedback to USP in October 2012, expressing concerns regarding the viability of the proposed implementation timeline, the need for alignment with ICH Q3D, and the regulatory implications of the new USP <232> and <233> chapters if they are not aligned at the time of official implementation. A request was made to consider delaying the official implementation date until it can be aligned with the implementation plans for ICH Q3D.

General agreement was expressed by the Coalition and in the individual comments by associations like GPhA on the need to update the USP standards in line with modern analytical techniques and appreciation was voiced for the significant pharmacopeial efforts to do so. However, the commenters stressed the need for the USP and ICH efforts to align in substance and timing, given the high impact of the changes across the drug development and market spectrum.

Supplier Communication and Risk Assessment Tools Offered

A recent project undertaken by the Coalition was to develop a “standardized information exchange request mechanism” for users and makers of excipients and APIs to begin discussing industry awareness of the developing elemental impurity requirements and share information about action plans being developed by pharmaceutical and ingredient companies.

The standardized information request form and cover letter is being widely distributed throughout industry, and it is hoped that it will be used to initiate detailed discussions regarding elemental impurities between makers and users.
of pharmaceutical ingredients.

The template has been developed to target the new ICH Q3D Step 2b guideline requirements and classifications. It is intended to facilitate value-added communication about elemental impurities and forestall the inundation of excipient suppliers with extensive and wide-ranging customer questionnaires that they may not be willing or able to complete and allow them to put together one meaningful reference form to provide to all their customers.

IPEC has now posted the form on its website (link provided below) and is encouraging its use as the most productive way for suppliers to provide the key information that users need to perform risk assessments and assess PDE compliance of their finished dosage forms.

The PDE calculator, another helpful tool developed by IPEC to support the risk assessment process, includes a fairly sophisticated set of spreadsheets that will allow companies to better understand the relationship between metals present in excipients and what would appear in the finished dosage form and the risks involved.

It would indicate, for example, that metals that may be present in an excipient might appear in a finished dosage form at too low a level to have any significant effect on the total PDE, and therefore would not be of concern. The calculator will be available for free on the IPEC website in the near future.

Bioavailability vs. Total Metal Content

The need to differentiate between the results of metal analysis done by total dissolution of the material with, for example, HNO₃ or HF, and extractables (acid leach) analysis done to determine bio-accessible metal content to the body through gastric simulation has been a long-standing concern of IPEC and the Coalition in the discussions on setting elemental impurity limits based on patient safety.

Perceiving that this extractables testing issue was not clearly resolved in the USP General Chapters or the new draft of ICH Q3D, the Coalition put together a comprehensive position paper to address it. The paper surveys related fields to demonstrate that the bio-accessible approach is the currently accepted standard across industries as well as in many USP monographs which include various specific metal analyses.

The Coalition’s concern is that the way the safety limits are presented in the ICH draft, when juxtaposed with the current USP general chapter coverage, implies that full dissolution of samples for total metal content would be required. Since bio-accessible levels are often significantly less than a total metal determination, especially for mineral-derived excipients, a full dissolution approach would entail an unnecessarily stringent safety margin.

The paper maintains that the use of total dissolution sample preparation techniques that would be necessary for some very insoluble mineral-derived excipients would create significant analyst safety risks in laboratories having to deal with reagents like HF. Since the use of acid leach sample preparation (bio-accessible) methods provide better simulation of actual safety risks to patients, the Coalition believes that there should be appropriate allowance for the use of these methods to determine PDE compliance.

The ICH limits, the Coalition is asserting, become truly “safety-based” only in terms of what can actually be absorbed in the body, and the risk assessment and related testing approach should be structured accordingly. The Coalition believes the issue needs further discussion in the compliance framework and will be making its case in commenting on the ICH draft guideline.

The paper collates the information and data on various extractable methodologies from the literature and makes recommendations – for example, on how the sample preparation concepts could be built into USP’s elemental impurities chapter <233>. The position paper has been submitted to USP for consideration and will be submitted to the European and Japanese Pharmacopeias and ICH in the near future.

While the issue is not addressed in the ICH draft or earlier USP chapter drafts, the Coalition believes that it is being considered for inclusion in the guidance document that FDA has been working on in the metals arena, which is expected soon.

Analysis Presents Challenges

Colorcon Global Regulatory Affairs Director David Schoneker, who has chaired the Coalition activities concerning elemental impurity issues and their ramifications in the excipient arena, emphasizes that while harmonized limits through ICH are a major step forward, significant challenges remain in the implementation process.

“It is one thing to establish limits. It is another thing to establish how you are going to actually do the testing or the risk assessment to determine compliance,” Schoneker commented to IPQ. “That is an area that is going to be a lot more difficult than previously expected, based on some of the analytical work that Coalition member companies have been doing.”

The complexities of the analytical work present many technical challenges, Schoneker stressed.
“We all knew that the testing and the analytical work was going to be challenging and complex.” However, as member companies do more sampling and testing against the new limits to determine method viability and actual levels which might be present in drug products, they “are finding out that it is going to be a lot more complex than anybody thought it was going to be” – particularly in terms of the analytical challenges that are matrix dependent.

A project team within the Coalition is now working specifically on these implementation challenges and what “needs to be considered, if you are going to do this testing and get accurate results,” Schoneker explained.

“That is an area that our project team is pursuing in a big way. They have intentions to do further publications and workshops regarding ICP [inductively coupled plasma] method challenges and solutions. The project team has asked a number of ICP experts to be involved on the team – these people are folks that have significant lab experience with ICP methods and understand how these tests work and any problems that may exist.”

USP and EMA Delay Guidance Implementation

The Coalition participants, in general, Schoneker explains, were pleased with the refinements that were incorporated by the ICH expert working group in the new Q3D Step 2b draft. He cited in particular:

- clarification that routine testing/control for the listed metals of concern is risk-based and may not be needed for some of the metals based on ingredient and process knowledge where available
- provision for different criteria for short-term as opposed to long-term dosing durations, and
- adjustment in some of the limits to make them more realistic.

Of the later, Schoneker cited the move away from an arsenic limit of 1.5 micrograms, which would have been a “major problem for a lot of companies,” to the more “realistic” and “tolerable” 15 microgram per day limit.

The Coalition was also pleased with USP’s decision to defer implementation of its elemental impurities chapters <232> and <233>, and a similar decision reached in Europe this summer to delay the application of the current EMA guideline on the specification limits for residues of metal catalysts and reagents to existing products until Q3D is finalized. The EMA guideline has been applicable to new products since 2008 and was to become applicable to existing marketed products on September 1, 2013.

Harmonization is what the Coalition has been seeking all along as the only viable approach to implementation of these requirements, Schoneker stresses. “Industry can’t implement multiple standards at different times for something as significant as elemental impurities. There really needs to be a harmonized standard that everyone is working with” and a reasonable and rational “implementation plan and timeline that is based on science.”

“We have moved a long way in that direction,” he said, but “there is still more that needs to be done” in terms of “clarifying the implementation process and understanding the analytical challenges ahead of us.”

“What we are really trying to do now more than anything in the Coalition is work together with the compendia and regulators to see how we can all facilitate the implementation in a way that is rational and that is really based in the science. We want to collaborate to find out what it really is going to take to implement this in the laboratory.” The tools and data that IPEC and the Coalition are putting together “are a first step in trying to do that.”

COLORCON’S DAVID SCHONEKER ON WHAT IS NEEDED FOR RISK-BASED DECISION-MAKING

In an interview with IPQ, Colorcon Global Regulatory Affairs Director David Schoneker discussed what is needed to achieve the risk-based approach the draft guideline calls for. Schoneker chairs the IPEC/Coalition efforts to help implement ICH Q3D.

Implementation of the Q3D requirements is going to be very a time-consuming and expensive project for all companies. The magnitude will depend on each company’s situation and what types of ingredients are used in their drug products.

It is going to require a lot of dedicated effort on the part of pharmaceutical companies to be able to gain the information
they are going to need to be able to make risk-based decisions concerning PDE compliance.

One of things that is not well understood by some people at this point is that, although ICH allows for risk-assessment outcomes to mitigate some routine testing, you can only do a risk assessment when you have some kind of data on which to base the risk assessment. The bottom line right now is that hardly any information exists on what the actual elemental impurity levels are for a lot of the excipients commonly used in drug products.

For synthetic excipients, it is probably going to be simpler to assess potential elemental impurity levels. But when you get into things like plant-based and mineral-based excipients, and you need to understand the potential levels for all of the Q3D metals, a lot of that information is simply not currently available, and it is going to be quite a while before it becomes available.

Most of that data is going to have to be put together by the pharmaceutical companies themselves. Very little of the data is probably going to be supplied by excipient companies, because for many of these companies the pharmaceutical business is a very small part of their market and they are not going to absorb additional costs for routine elemental impurity testing. Many companies will provide excipients for pharmaceutical uses but will not test for elemental impurities or agree to meet specific specifications that are any tighter than what they have historically agreed to.

In many cases I know the pharmaceutical companies already are doing a lot of testing to try to get some baseline information on what they might anticipate for some of these materials. And that information may ultimately be able to be used in a risk-assessment. This type of risk-assessment, however, will not be easy to do in the short term due to unknown unknowns.

The real difficulty comes when you get to things like mineral-based materials that come from mines etc. Risk-assessment counts on some level of predictability. So to do a risk-assessment, you can’t just say ‘I have tested ten samples and all of them look like they didn’t have anything present or are less than one part per million.’ That might work for a synthetic material that has process predictability and a purification process in place, but for a mined material, the variability that might exist is a complete unknown. When you dig in one portion of a mine versus another portion of the mine, it is not ever going to be predictable. You might test 1000 samples of that material this year and every one of them says it is less than two parts per million. That gives you absolutely zero ability to predict that the next sample that you are going to receive might not be nine parts per million.

I am not so sure that it will be possible for risk assessment to mitigate testing by the user for those kinds of materials, because the user is never going to get to a point, nor are they going to be able to get information from their suppliers, in many cases, to be able to do an appropriate risk-assessment, unless they have a metal where they truly do have a worst-case scenario type of specification.

For example, if the level of lead in an excipient has historically been less than ten parts per million for the last ten years, and the supplier has data to know that they never vary more than that, the supplier still can’t guarantee that the level of lead will be anything lower than that. If you use ten parts per million as a worst case specification for that excipient in your calculation for your drug formulation using the PDE calculator and it still turns out that the lead level is less than the PDE, then in that situation you can mitigate some testing. For that material in your particular formulation the lead level may not matter. There will be limited sets of circumstances however, where you can make those kinds of decisions without having significant test data.
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