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.
Transformation in Industry Practice Must Accompany FDA’s Generics Program Overhaul to Meet GDUFA Goals, OGD Stresses

A core message emerging from the presentations by FDA management at the GPhA/FDA Fall Technical Conference in Bethesda, MD in late October is that the transformation underway in the agency’s generic drug review program will need to be matched by an equivalent transformation in industry practice for the goals of the Generic Drug User Fee Act (GDUFA) to be achieved.

Providing a summary report on FDA’s progress in implementing GDUFA at the conclusion of the conference, Office of Generic Drugs (OGD) Acting Director Katherine “Cook” Uhl stressed the “game changing” nature of the act. Its implementation, she pointed out, is a “monumental task” that requires “a quantum leap” at the agency and in the industry to be successful.

The OGD leader highlighted the “huge” efforts underway at FDA to implement the changes needed to decrease Abbreviated New Drug Application (ANDA) approval timelines from 34 months to 10 months, and underscored the need for industry to transform its practices as well.

“I think the key take home message,” she said, “is that FDA and industry – the key word here is ‘and’ – have to do this together.”

Fundamental to GDUFA’s success will be industry improvement in the quality of its ANDAs, Uhl stressed.

“The industry motto has been, ‘file first, develop later,’ she said – an approach resulting in poor quality applications that lead to multiple review cycles. Continuing this model would result in “an exceptionally inefficient use of GDUFA resources. We really need improved quality of submissions and decreased review cycles.”

Decreasing the review cycles is critical to the agency’s ability to meet the 10-month review goal and get generic products on the market more quickly as mandated by Congress and stipulated in FDA’s “commitments letter.”

Commitments Letter a “Must Read” for Company Management

Uhl emphasized that it is imperative for generic firms to become very familiar with the GDUFA commitments letter so they understand the full dimension of the changes and the role they need to play.

In turn, she advised the GPhA/FDA conference attendees that senior management needs to be briefed on the GDUFA goals and commitments and the company responses required.

The importance of being familiar with the commitments letter was also highlighted as a key take-home message from the meeting in the summaries provided at its conclusion by Roxane
“If we get caught off guard on some of this stuff, it is going to be our heads – those of us in regulatory affairs,” Macdonald stressed. She urged attendees to “take the information back and make sure your senior management knows and understands the new challenges, the new dynamics.”

“Make [senior management] read the commitments letter,” she continued. “Make sure there is an understanding within your organization and that they are prepared for the new world we are all facing here…. It is a brave new world and let’s take the steps to go there.”

**Uhl Highlights What is Needed from Industry**

Uhl’s update at the GPhA/FDA conference encompassed:

- GDUFA goals regarding cycle times, controlled correspondence, dealing with the application backlog, and hiring and training of staff
- Implementation challenges including re-writing all internal procedures to support the shortened review timelines
- Industry changes that need to occur
- GDUFA accomplishments to date, including having met or surpassed all GDUFA year-one goals
- OGD FY2014 priorities – i.e., what is needed to “operationalize” GDUFA, and
- OGD FY2014 challenges, which include hiring and training staff, relocating to FDA’s White Oak campus, and getting the cooperation it needs from industry to make GDUFA successful.

[Editor’s Note: Uhl’s remarks are provided in full below.]

Uhl explained that although GDUFA will require a “paradigm shift” for FDA’s generic drug program and the industry it regulates, the end result will be that the processes will mirror those already in place for new drugs under PDUFA. She laid out the new expectations for industry and explained why they were needed (see box above right).

Regarding agency goals and changes that it will need to make under GDUFA, Uhl pointed to the need to deal with the current application backlog and to get a better handle on the numbers and locations of the firms it regulates.
making Complete Response (CR) letters as complete as possible with no more “piece-meal” deficiencies ● not issuing division-level deficiencies in CR letters ● instituting “easily correctable deficiencies” (ECDs) that are separate from major or minor deficiencies, and ● greatly increasing the number of regulatory project managers as single points of contact for applicants.

Uhl noted that there has been “a misinterpretation or a supposition from industry” that if a firm gets ECDs it will not get major or minor deficiencies. She explained that they are “entirely different things.” The ECDs are, as implied, easily correctable and communicated separately, whereas major and minor deficiencies will appear in CR letters.

First Year GDUFA Goals Met

Uhl reported in her GPhA/FDA address that FDA met or exceeded all of its first-year GDUFA goals, which she characterized as “emblematic of the agency commitment to being sure that this program is a success.”

She also pointed to a key industry accomplishment – paying the GDUFA fees that will fund the program. The agency estimate was $299 million dollars, and what was collected “was pretty darn close to this.”

FDA met its year-one goals regarding: ● hiring ● clearing the application backlog ● issuance of CR letters ● promulgating guidances ● updating and improving its website ● enhancing its regulatory science program, and ● completing day-to-day work.

The agency has established a GDUFA website (www.fda.gov/gdufa) that includes links to a variety of related information and forms, including the commitments letter, guidance documents, the arrears list, user fee schedules, webinars, and lists of registered generic drug facilities and drug master files available for reference.

Regarding the day-to-day work that needed to be done in addition to meeting GDUFA goals, Uhl noted that OGD approved over 425 applications – somewhat less than the previous year – as well as “many more” prior-approval supplements than the previous year.

In addition, the office issued over 60 new bioequivalence guidances, 40 revised bioequivalence guidances, and a stability guidance and accompanying Q&A – none of which were required by GDUFA.

“Operationalizing” GDUFA

In her concluding remarks, the OGD leader outlined the goals and challenges the agency faces in moving into year two of GDUFA and making it functional, including key reorganization efforts that are underway.

The Office of Pharmaceutical Quality (OPQ), she explained, will consolidate all of the CMC and micro functions for the entire center under one office, including the OGD chemistry divisions, the DMF group, and the micro group.

OGD will be reorganized into a separate super office in CDER, putting it on parity with the other super offices that have user fee programs. It will have an office of research and standards – the only user fee program that will have a regulatory science component. It will also include an office of bioequivalence with three divisions and a division of clinical review, creating more clinical presence in the Office of Generic Drugs.

The reorganization will also result in an office of regulatory operations, which will include: ● a division of project management ● a division for labeling review ● a division of filing review, and ● a division of quality management systems.

Uhl characterized the challenges for FY 2014 as a “huge lift” and a “monumental task,” requiring “transformational change.”

Key challenges for the agency include hiring and training new staff, dealing with the complexities of an increased budget, and relocating to FDA’s White Oak campus.

Characterizing the ability to hire as “a great thing to be able to do,” and juxtaposing it against the more typical unfunded mandates that come to the agency, Uhl emphasized that the hiring process is nevertheless challenging and time-consuming.

The budget changes, while welcome, are also challenging, with a “small” administrative staff overseeing a six-fold budget increase. The increase is in part due to the hiring of new staff. However, she noted that there are also challenges associated with finding places to locate the new hires.

The OGD director commented that the move to White Oak has created “a phenomenal amount of angst among the staff.”

To help quell the anxiety, she is telling her staff that “this will be my third move to White Oak. I am still alive. I survived it. And I survived it so much that I want to do it again. It is not the end of the world. As a matter of fact, it will be exceptionally beneficial to OGD to have us at White Oak, where all the other components of the generic drug program are. This will be very good for us.”

Six Month Lead Times Needed for DMFs

Joining Roxane’s Amann and Impax’ Macdonald in providing summaries of the discussions at the conclusion of
the GPhA/FDA conference was Perrigo Global Regulatory Affairs VP Richard Stec.

All three have been actively involved in the GPhA dialogue with FDA on GDUFA and its implementation. They reviewed the various meeting sessions for which they served as moderators.

Stec, who moderated the preconference workshop on drug master files (DMFs), focused on some of the key points that emerged in the discussions.

Echoing Uhl in stressing the significance of the mandate beginning October 2014 that ANDAs will receive a refuse-to-receive (RTR) designation if they reference DMFs for which a completeness assessment has not been finished, he reiterated the recommendation that DMF holders should submit their applications six months in advance to clear the process.

The Perrigo official explained that, while first-cycle DMF reviews are taking on average 69 days, if “you put that together with the number of DMFs that have cleared in a single cycle, which is only about 14%, it is fair to say that to provide adequate lead time so that you don’t risk an ANDA getting a refuse to receive, six months lead, I believe, is a fair estimate.”

Stec also stressed the transition from a three to a two-tier DMF priority categorization in January 2014. One tier will be DMFs receiving priority attention based on being referenced in an ANDA that has been granted a priority review, and the second, “normal” category will encompass all others.

Another key FDA concern is the need to transition to electronic DMF filing.

“Currently only about 18% of DMFs are being submitted electronically, and that is costing time within the review process to get the DMF cycle through and to get on the reference list.” As such, Stec encouraged “ANDA sponsors to work very closely with your supply partners to get the DMFs submitted electronically.”

Stec also addressed the use of teleconferences after receiving complete response letters to clarify the questions asked either regarding the DMF completeness assessment review or the ANDA review.

FDA’s data indicates that there have only been four teleconferences asked for regarding DMFs, he noted, while up to 200 were agreed to in the GDUFA negotiations.

Stec encouraged the use of teleconferences when needed to prevent an additional review cycle, commenting that “we are paying for them – they are available to us.”

The Perrigo official echoed comments made by Lachman board member Robert Pollock at the conference on the unworkability of the five-day turnaround time FDA has put forward in its draft RTR guidance for responding to CRs that contain fewer than ten minor deficiencies. Pollock provided an “industry perspective” on the RTR draft, which was out for only a 30-day comment period during the month of October.

“The five-day turnaround time may be doable for a domestic business,” Stec said, “but the generic industry is not a domestic business. We are very, very globalized. Five days in managing through bank holidays and religious holidays is going to be extremely difficult and I feel will generate unnecessary refuse-to-receives.”

**Dialogue on Quality Metrics Continues**

Amann pointed to the “tremendous changes” highlighted by Uhl and CDER Director Janet Woodcock, noting that “one of the biggest changes is actually the reorganization that is going to occur and hopefully be completed in 2015.”

The Roxane official highlighted the amount of activity that is ongoing regarding quality metrics and quality compliance.

While there are quality metrics that are already being routinely deployed by industry, the problem is “that every company probably has a slightly different definition of those metrics.” The metrics will have to address three important things, Amann pointed out: • the organization • the process, and • the policy.

The result of the discussions that will now be taking place, he said, is that “expeditious approval will require quality metrics for the manufacturer…and lead us hopefully into regulatory relief in the future. So I think embrace it and live with it, because it will be coming and I think it will be very good for all of us.”

[Editor’s Note: At GPhA’s CMC Workshop in June, CDER Director Woodcock and Office of Pharmaceutical Science (OPS) Scientific Coordinator Russ Wesdyk gave presentations on the Center’s intensified focus on quality and its quality metrics initiative, respectively. See IPQ Monthly Update June 2013 pp. 2-20 for in-depth coverage of their presentations and the discussions that followed. Both Woodcock and Wesdyk provided updates at the GPhA/FDA conference in late October.]

**Stability Email Box Recommended**

In her summary remarks, Macdonald focused on the stability and project management discussions at the conference.
Along with FDASIA and the commitments letter, she urged attendees to also read FDA’s stability guidance and Q&A as well as the ICH stability guidelines “to ensure compliance as it pertains to stability.”

The Impax official noted that the agency now has in its hands the comments submitted to the docket on the Q&A. The comments, along with the discussions at the conference, she said, provide “a great pool of information that can now be used to perhaps make that stability Q&A document a living document that can be an ongoing summary of the questions that we have…and a mechanism to ensure that we have a high quality application that does meet all the expectations and the timeframes associated with GDUFA.”

Macdonald highlighted, in particular, the suggestion made at the conference by Apotex Regulatory Affairs VP Kiran Krishan to develop a stability email box similar to that being used in the DMF context, which has been “a great success.” The approach, she said, would keep down the flood of redundant emails from individual companies and “help get us through the next year or two as we learn how to operate within the new paradigm and the stability expectations.”

A clear message emerging from the conference based on the number of questions arising and FDA comments, Macdonald pointed out, was “how key” the 356h facilities form is and the importance of “making sure that it is an appropriate document going in.” FDA’s RTR draft guidance, which includes a section on 356h, should help eliminate some of the problems that could generate RTRs, she said.

Macdonald also highlighted the theme of the need for heightened communication and transparency to ensure the rapid launch of generics on the market.

However, of concern from an FDA project management perspective is that the ability to meet the expectations of the GDUFA commitments letter could be jeopardized by too many calls coming in from sponsors as approval nears.

She referenced a comment by OGD Special Assistant to the Director Tom Hinchliffe indicating that the regulatory policy group is working on some policies that “might address ways to facilitate the communication needs on both ends to meet all of our goals.” GPhA, she affirmed, would commit to helping create “some guidance and some policy that works for both of us.”

DOWNLOADS FROM THE STORY:
- GDUFA website
- GDUFA commitments letter
- OGD “refuse to receive” draft guidance
- Meeting minutes from OGD/GPhA Board of Directors meetings

OGD’S KATHLEEN UHL ON “LIFE WITH GDUFA”

At the GPhA Fall Technical Conference in Bethesda, Maryland in late October, Office of Generic Drugs (OGD) Acting Director Kathleen “Cook” Uhl provided insights on the “game changing” impact that GDUFA is having on the agency and the industry. Uhl highlighted many of the initiatives that received further attention from other OGD officials during the course of the GPhA conference. After an overview, she addressed:
- GDUFA goals
- implementation challenges
- industry changes
- GDUFA accomplishments
- OGD FY2014 priorities, and
- OGD FY2014 challenges.

The Hatch-Waxman Act was enacted in 1984. I started medical school in 1984. So you can do the math for how old I am. During my entire professional career I have used generic drugs, dispensed generic drugs, and treated patients with generic drugs. I did most of my clinical work in the military. As many of you know, the DOD [Department of Defense] is a huge purchaser of generic drugs, so I am a staunch advocate for the importance of generic drugs in this country.

Now a little bit about the life under GDUFA: Several people I know from my previous positions in FDA have come up to me and said, ‘jeez, Cook, do you need your head examined?’ for taking this position. I do not have a good psychiatrist, but I do believe in good drugs.

I will say this is definitely one of the most challenging jobs I have ever had in my professional life. I am busier than I have ever been since I was a resident, back in the days when there were no restrictions on residency hours and we worked over 100 hours a week.

That said, this is by far the most interesting initiative that I have ever been involved with. The importance to the public health of the American people is imperative. I actually consider myself privileged to be part of this ‘life with GDUFA’
and getting GDUFA off the ground.

**Overview**

So with that, let’s move in to what I am going to talk about today…. I just want to give you an update on GDUFA and an update on the Office of Generic Drugs.

We have heard about this, but I want to emphasize it again: GDUFA – lots of changes. There are increases in a variety of things: responsibility, commitments, obligations, accountability, quality, etc. But I think the key take home message…is that FDA and industry – the key word here is ‘and’ – have to do this together.

GDUFA is a major game-changer. There is no doubt about it. It is a quantum leap. It is of epic proportions. Even one of your bloggers called certain things we have said ‘asking the tiger to change its stripes.’ But I will echo what [Mylan VP Marcie McClintic] said yesterday: GDUFA is and requires a transformational change at the agency and in the industry in order for this to be a successful program.

And here are just some examples of what I am talking about: There are huge changes to the generic drug program at FDA. There have to be substantial changes to the generic drug review within OGD, and I am going to walk you through this a little bit…. There are obvious changes in how we communicate with industry and changes to the inspectional component….

But are there changes for industry? Absolutely. The quality of your application has got to change. The number of review cycles has got to drop. I will walk you through why, because it is obvious that a lot of you have not read the commitments letter, so it is not obvious to you then why there need to be changes in the number of review cycles….

I know, I recognize, [CDER Director] Dr. Woodcock recognizes, that there are high expectations, huge expectations from industry, especially because you guys have already paid your money. You have paid and what are you getting out of this? We know that. We recognize that. We hear you. We are fully dedicated to getting this program up, operational, functional, and more importantly, successful.

The first step was…getting the fees in and creating that infrastructure to receive the fees. Because without the money, we cannot hire the people, we cannot build the electronic systems that [Office of Strategic Programs Director Theresa Mullin] talked about. Now we are moving into the next phase, which is operationalizing and implementing GDUFA. I said this yesterday, I will say this again, and I will continue saying this for as long as I am standing up here in any functional capacity with OGD: We are in this together. Because only together can we accomplish the goals that GDUFA has put forward.

We cannot succeed if we just throw the money and throw the FTEs at doing the exact same thing. Almost every single thing written into GDUFA is something new and different for the agency. And so continuing to do just the same thing is not going to get us there. In order to meet these exceptionally aggressive timelines and timeframes, this requires mapping out the process. What is the review process? What is the interaction between the review side and the inspectional side?

[We need to] map that whole thing out, which prior to GDUFA was a 34 month time-frame – map out the process, identify the redundancies and interdependencies…and then move to process improvement. How do we improve that process so we can get to 10 months? And then what is the strategy in order to reach those goals and to make the metrics that are required under GDUFA? And as I said, we need to implement and operationalize this.

I have used this in one of my all-hands meetings. I thank Glen Smith, who is one of the chemistry division directors, for giving me this. This comes from one of those organizations that has those ‘demotivational’ posters that are very funny as well as apropos. But I do not do this tongue-in-cheek.
I actually say this to people in the office: I ask, ‘why do we do something?’ And they say, ‘well, we have always done it that way.’ That is not a good enough answer. ‘Why do we do it that way? Just because you have always done it that way does not mean that it is not incredibly stupid.’ And it also does not mean that it is not incredibly inefficient as well. And so we really need to think through, not just why are we doing something, but how we are doing it. How is what we are doing going to get us to meeting these goals under GDUFA?

**GDUFA Goals**

You have seen this already – the [GDUFA website](#). You have heard about the commitments letter. I am not going to ask people to stand up, but did anybody go to the GDUFA website last night…and try to find the commitments letter? A couple hands went up, not a whole lot.

This is probably the agency’s number one priority – GDUFA. We take congressional mandates very seriously. And we are hoping, because we are in this together, that you will take these commitments very seriously as well.

So I will again say to you what I say to all the staff in OGD: You need to read the commitments letter. You probably need to brief your more senior management on what GDUFA is. What are the goals? What are the commitments? What is it that you need to be responsive to and about? You do not have to do any homework on that because you have a whole bunch of slides that we just did over the last three days that you will be able to use to brief your upper management.

You have seen the slides about what the performance goals are. The goal at year five is that ninety percent of the original ANDAs will have an action in 10 months. An action means an approval, a tentative approval [TA], or a complete response, a CR. There is a tremendous amount of information in the commitments letter about the different tier amendments. I do not have time to get in to them. There are timelines as well for prior approval supplements [PAs].

The backlog: That is another big thing. I know you guys are worried about the backlog. The goal is that 90% of the backlog has a first action by the end of year five. I will show you the progress we have made on that.

And controlled correspondence: I hear a lot of grumbling about controlled correspondence. ‘We are not hearing from you,’ etc., etc., etc. There are actually no metrics for controlled correspondence until next year, year three – and that is that we address 70% of those within four months. By year five, our goal is that we address 90% of them within two months. Right now, there are no GDUFA goals on the controlled correspondence.

### GDUFA Review Performance goals

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<tr>
<td>Original ANDA</td>
<td>Expedite review of paragraph IV and maintain pre-GDUFA productivity</td>
<td>60% in 15 months</td>
<td>75% in 15 months</td>
<td>90% in 10 months</td>
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<td>Tier 1 first major amendment</td>
<td>Maintain pre-GDUFA productivity</td>
<td>60% in 10 months</td>
<td>75% in 10 months</td>
<td>90% in 10 months</td>
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<td>Tier 1 minor amendments (1st – 3rd)</td>
<td>Maintain pre-GDUFA productivity</td>
<td>60% in 3 months*</td>
<td>75% in 3 months*</td>
<td>90% in 3 months*</td>
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<td>Tier 1 minor amendments (4th – 5th)</td>
<td>Maintain pre-GDUFA productivity</td>
<td>60% in 6 months*</td>
<td>75% in 6 months*</td>
<td>90% in 6 months*</td>
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<td>Tier 2 amendment</td>
<td>Maintain pre-GDUFA productivity</td>
<td>60% in 12 months</td>
<td>75% in 12 months</td>
<td>90% in 12 months</td>
<td></td>
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<tr>
<td>Prior approval supplements</td>
<td>Maintain pre-GDUFA productivity</td>
<td>60% in 6 months*</td>
<td>75% in 6 months*</td>
<td>90% in 6 months*</td>
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<tr>
<td>ANDA, amendment, and PAS in backlog on Oct 1st, 2012</td>
<td>Act on 90% by end of FY 2017</td>
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<tr>
<td>Controlled correspondences</td>
<td>70% in four months**</td>
<td>70% in two months**</td>
<td>90% in two months**</td>
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*10 months if inspection required  
** One additional month added to goal if clinical division input required
There are a variety of other performance goals that we have: ● hiring and training of staff ● DMF completeness assessment ● the enhanced refuse-to-receive [RTR] guidance, and ● a variety of different teleconferences. . . .

I know there is a lot of concern about the inspections. Again, getting to the biennial inspections with a risk-based surveillance is a five-year goal. There are no interim metrics on that until year five.

[At this conference you have heard about] a variety of other efficiency enhancements [including inspections, systems, and electronic standards.]

I do want to highlight the difference in the user fees, because what I have heard since my tenure here in OGD is, ‘well, why are you treating the generic industry differently? We feel like we are not being treated fairly, etc.’ The user fees are substantially different between the NDA world and the ANDA world. And I just have here what the new user fees are for FY 14.

Another requirement under GDUFA was this aspect of ‘self-identify.’ And you guys did that, and we thank you very much for doing so. Now we at least understand the lay of the land so that ORA and compliance can target all of the facilities on a rotating basis to be sure everything gets inspected in an appropriate time-frame using a risk-based model.

But I think what you really want is for us to get it out the door and get it back to you. I just want to highlight for you how much freight we really have to move, because I think it paints the picture of, ‘wow this is really a huge program.’

The GDUFA backlog is over 4700 applications. And that all needs to at least have a first action by the end of year five. But we have received over 1000 new ANDAs last year – much more than expected per the commitments letter.

We received 1400 distinct DMFs. That was way more than what we anticipated getting. We had over 5700 supplements – a lot more than expected. We received almost 2000 amendments. And we have received pretty darn close to 1000 controlled correspondences in one year alone. That is a substantial amount of freight that we need to move down the tracks and respond to you guys, now under GDUFA with timelines and goals. . . .

The thought of GDUFA and the generic drug program has historically been that it is OGD’s bailiwick, and that is definitely not the case…. This program has every single component of CDER involved in it and multiple components of the Office of the Commissioner and ORA. The office of generic drugs is really just the interface with the applicant to get those applications through the system and hopefully approved. . . .

The GDUFA steering committee has representation of every single super office in CDER on it as well as senior management for ORA – a commitment to you that this is a high priority program in the center and in the agency.

This is the intense effort that the staff in OGD is doing – meeting every week, if not several times a week, to map out the generic drug review process and how it interfaces with all the other components of the center and the agency. And
then working to not just map those processes, but then streamline those processes such that we have got a process that is going to make us meet those goals.

So all of the freight…needs to be put through some kind of system that gets us to meet the goals and be successful in all the metrics for GDUFA.

### GDUFA Implementation Challenges

I want to change gears a tiny bit and talk about some of the changes and the challenges in OGD related to GDUFA implementation.

**Complete response letters:** At first I thought it was silly that I had verbatim language from the commitments letter in a set of my draft slides. But after yesterday and the small number of you that stood up [indicating you had read the letter], I made sure that last night when I was finally tweaking my slides that I kept this in here: ‘FDA will issue complete response letters, rather than discipline specific letters, for all ANDAs. Complete response letters will reflect division level review of deficiencies from all relevant review disciplines, including inspection.’

There was a question I remember from yesterday where someone asked: ‘Will we go back to issuing discipline specific deficiencies?’ First of all, ‘back’ is not in my vocabulary. We are moving forward implementing GDUFA. So I can guarantee you that we will not be issuing division-level deficiencies, because we have to do complete response [CR] letters. Now I will make a caveat to that when we get to the easily correctable deficiencies in a subsequent slide.

The goal here is that we, FDA, give you a complete response letter that is as complete as possible – no more piece-meal deficiencies. You will get the deficiencies across the entire review program. It will contain major and minor deficiencies. This required some pretty substantial changes in our internal processes and policy. We had to create enduring training materials. Because as you know, one of the big things in GDUFA is hiring, so you cannot implement new procedures without being ready to train the new people from the day they walk in.

This is a huge paradigm shift for FDA as it relates to the generic drug program. This is not a huge paradigm shift for anyone in the agency involved in new drugs, because the new drugs [program] has been doing CR for a number of years. This is a major paradigm shift for OGD, and I know this is a major paradigm shift for those of you in industry.

Another component of the commitments letter is easily correctable deficiencies [ECDs]. So here is where you will get discipline-specific deficiencies: ‘Reviewers will make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in the ANDA.’ The goal here is that the reviewer can finish his or her review so we can move the application down the path and get it to completion within the GDUFA metrics. The interesting thing is that there is no definition of what an ECD is in the commitments letter, and that is challenging.

I again want to point out that if it is a major deficiency or a minor deficiency, it is not an easily correctable deficiency. So the only things that will be communicated via this mechanism are ECDs. The majors and minors will be received by you in a CR letter. But in order to do this, we had to change a whole bunch of our internal and external processes and policies.

We had a guidance that needed to be revised that we are in the process of revising [along with] a MAPP [Manual of Policies and Procedures], internal SOPs, etc. What I would like to point out to you here is the dates on these: Every single one of those processes pre-dates the date that GDUFA went into effect. So we cannot be using processes that do not get us to a 10 month goal date. All of these processes need to be revised. We need training materials. We need enduring training materials and communications.

We have really beefed up our regulatory project management staff. We will have an entire division of regulatory project managers [RPMs] in OGD. In the past, the project management was exceptionally siloed – it was basically per discipline. And essentially there was no one responsible for your applications from the time they came in the door until the time they left. There was no central point of contact. And that is absolutely imperative under GDUFA as we are under exceptionally tight timeframes. Someone has to be responsible, basically from soup to nuts, and that is the RPM. They are your major point of contact. They are the point of contact.
This allows us to centralize our communication flow. It allows for consistency. It streamlines processes and all of that kind of stuff. These people are and will become the regulatory experts for the Office of Generic Drugs. What this does is it allows the reviewers to do what their job is, and that is to review. Because you want those reviews done, the disciplines finished, so that you can hear from the agency whether your product can be approved or what are the deficiencies.

And I would like to point out that this is not anything new. I did not cook this up on my own. This is what the rest of the center does. This is consistent with other product centers and other user fee programs. So this basically puts the generic drug program in step with the rest of CDER and the rest of the agency.

**Status updates:** I have heard from numerous people since I have been here. I actually get emails on a pretty regular basis. [OGD Supervisory Chemist Bob West], I think, has been inundated with comments at this meeting. We absolutely hear you. I acknowledge the importance of these updates to you, and your desire to be able to launch on day one. We value your constructive input and collaboration on how we can do this under GDUFA because, again, we cannot go back. The past practice in OGD was very reactive. It was a crisis management mode. It was a fishing expedition on your side – shopping around until somebody would tell you where your application was. Or it was fifteen different people telling you where your application was with fifteen different answers.

What else happened is OGD basically sold out some of our other agency colleagues by saying, ‘well, we are done, but they are not,’ and pointing the finger at somebody else. That is not acceptable. We cannot continue that practice. We need to move forward to a new practice here that is proactive – a systematic process that meets the goal dates. That is what we have to do. We have to figure out how to do that.

We are working on it. Again, we hear you. We know the importance of this. We have quarterly meetings with the GPhA board of directors. This has been a topic in every single one of them, and I am sure it will continue to be a topic until we come to some agreement on what this is going to look like.

**Industry Changes**

So let me walk you through a little bit of what I see as some industry changes under GDUFA.

This is a commitment between FDA and industry, so this requires changes for both of us. But I will posit the question to you, ‘what are you doing differently because of GDUFA?’ – I just walked you through several things that we are doing differently because of GDUFA – and how is that going to get us to meet these goals? And if you aren’t doing anything differently, how is that lack of change going to get us to meet these goals?

So we are requesting the exact same thing that we are giving you. We want a central point of contact. We want one person who is your point of contact for your application. And again, this is not unique to an ANDA. This is what other product centers do. This is what the other user fee programs do. This puts us in step with the rest of the center and the rest of the agency.

We need you to shore up your business partners. There was mention yesterday of the ‘arrears list.’ It is imperative that you know who is on that list – whether your suppliers are on that list or not. Because if you submit your application and they are on the list, your application won’t be received. You need to have whatever kind of confidentiality agreements there are that allow us to then be able to talk to some of your contractors.

An example that I have here is a letter of authorization with your API suppliers or sites. If you do not have that confidentiality agreement and you are concerned about the status of, say, their inspection, and you want us to talk to you about it, we cannot do that without appropriate authorization.

Your submissions need to be electronic if you want the GDUFA goal dates to apply. If it is a paper submission, the goal dates do not apply. And if that is a surprise to you – and when it was mentioned this morning, I did hear some grumbling behind me – it enforces the need for why you need to read the commitments letter. And it needs to be submitted in an eCTD format, not a PDF.

In addition, you need to ensure that the 356h is accurate, complete, and identifies all of your sites. Why is that?
Remember, now we are moving towards a ten-month clock. If all of your sites are not identified, and if you identify them many months down the road, that will probably preclude your approval at 10 months. Why? Because those sites, that form, will upload into other systems at the agency. It will inform ORA and compliance about all the sites, so they can schedule the inspections.

[Regarding] the DMF [drug master file] completeness assessment: [OGD DMF Supervisory Chemist Dave Skanchy] and his group did a fabulous workshop on Monday. This was also alluded to in the discussion about the RTR earlier today. The DMFs should be submitted well in advance of the ANDA in order for that assessment to be conducted. We are saying six months. That is a guesstimate, quite frankly, based on the data that we have for how long it takes to do the completeness assessment, get the response back from the DMF holder about any deficiencies, and to be able to have that completed.

Right now, you are getting a free pass on this. We raised this situation to our senior-most lawyers in the agency and their advice is that we should not implement that in years one and two. But in year three, if your DMF comes in with your ANDA, you will get an RTR.

I am going to walk through the [simplified ANDA review process] very quickly. This is a very simple ten-month time frame for what has to happen. You have to have the filing review quickly, within a couple months, and the DMF completeness assessment, and then followed by the inspection scheduled and done, and the discipline review. If that DMF assessment goes out to six months or later, that means that we have only a couple of months to do the remainder of the activities, and it will not be feasible to do that. It is our advice to you that you should submit them six months before you submit your ANDA application.

The complete response letters: This is what we need from you when you respond to a complete response. Your complete response to the complete response – that all deficiencies that are in the CR need to be addressed in your submission. If not, it is a partial submission, and partial submissions will not be accepted – they won’t be processed and they won’t start a new submission cycle.

And your response needs to be timely. The complete response letter has to come to us within a year. The office has been exceptionally lax in enforcing 21 CFR 314.65 – extremely lax. There are applications pending for you guys for years. And we will move forward on administratively withdrawing those applications. We will not start that eminentely, but there are discussions in the works. We are going to move towards that model. That is the model with which other user fee programs operate. That is what happens in the NDA world. Otherwise, this is really abusing the system. It is wasting the GDUFA resources. It is basically your competitor getting an edge on you with your money.

This is the paragraph that is in every single CR letter that goes out: ‘Within one year after the date of this letter, you are required to resubmit or take other actions available. If you do not, we may consider your lack of response a request to withdraw the application.’ So we are going to start holding you accountable for this part. In addition, FDASIA – the legislation from last year which GDUFA is part of – requires the agency to report to Congress not just what is pending us, not just things we still have to do, but what is pending you guys and the length of time.

Easily correctable deficiencies: The goal here is that we want the reviewers to finish the reviews so we can get the application out and get any of the deficiencies back to you or get you a TA or an approval. We need a very timely response. We need your response back to us within 10 business days. The goal is to get the reviewer to finish the review. It moves us towards an action.…

[OGD Special Assistant to the Director] Tom Hinchliffe told me from the project management forum earlier in the week
that there was a misinterpretation or a supposition from industry that if you got ECDs, you would not get major or minor deficiencies. They are two entirely different things. The ECDs are just that – easily correctable deficiencies. Major and minor deficiencies will roll up into your CR letter.

This is the part that I want to implore the most: The industry motto has been file first, develop later. And what we get then are poorly assembled applications – poor quality applications that lead to multiple review cycles. If this model continues, this is an exceptionally inefficient use of GDUFA resources. We really need improved quality of submissions and decreased review cycles.

And this is an illustration of why…. In the tiered amendments, basically, the first major amendment that you submit has a ten-month review clock, and there are five minors that you can have anywhere from three to six months – that is the GDUFA goal. But if it is your second major amendment or more, there is no GDUFA goal associated with that. So if it is the second major amendment, there are no goals.

**GDUFA Accomplishments**

Let me walk you through some of the accomplishments. There has been a tremendous amount of activity at the agency around GDUFA.

First of all, here are your accomplishments. You guys paid the fees, and we thank you very much. The estimate was that there would be $299 million dollars collected, and what was collected was pretty darn close to this. And you guys self-identified, which will really help with the five-year aspect of the inspections, the biannual inspections and risk-based inspections.

Now I want to walk you through a bit of what FDA’s accomplishments are. We hit every single year one deliverable. In case you did not hear that – every single year one deliverable. And just because I want to really be sure you have the take-home message – every single year one GDUFA goal, the agency hit. My reason for emphasizing that is because I think that is emblematic of the agency commitment to being sure that this program is a success.

The goal for hiring for year one was that 25% of those hires would come in – over 950 hires to the agency under GDUFA. The agency actually exceeded that goal.

The backlog: The numbers show the GDUFA backlog: [2866 original ANDAs, 1882 PAS supplements]. It is a fixed number. It does not change. First action – a first action is a CR, an approval, an ANDA, RTR, or a withdrawal – we issued first actions on over 1600 applications in the backlog. So 35% of the backlog has already been addressed. We have already met that GDUFA metric of 35%. We still have a long way to go. We still have many more applications to get through. The majority of those were CRs with inspection. The next in numerical form are the approvals or the TAs. But the CRs with inspection are by far the greatest amount that we did.

Complete response letters: We issued over 1250 complete response letters. The majority of those were for the backlog. But I really want to point out to you what it took to stand up this effort in OGD, because the prior year, the year before GDUFA, we issued less than 50 CRs. And last fiscal year, FY13, we issued 1250 CRs. About 560 of those were with inspections – those were the ones that hit the GDUFA metric.

But more than those, 690 that did not have inspection, we sent those results to you. We actually argued with our senior-most lawyers to say, ‘this is an important thing for companies to get.’ It gets to this aspect of communicating with industry and demonstrating transparency. But if we really wanted to follow the letter of GDUFA, we could have not issued those and waited for inspections, which for some of them might be several years down the road. So 690 do not even meet the metrics.

We issued a whole bunch of GDUFA guidances: • two Q&A guidances • the DMF Completeness Assessment • Refuse to Receive, and • guidances on the fee types. These are the only guidances that are required by the GDUFA commitment letter. But you heard [OGD Regulatory Counsel Keith Flanagan] up here yesterday saying that we are going to issue more guidances. It is obvious to me and to several other people that in order to really help you improve the quality of your submissions and reduce the number of cycles that we are going to have to provide you with more specific agency guidance. We are committed to doing that.
And this whole aspect of **communications**: You know about the website. You know about AskGDUFA. We have the GDUFA listserv. And there are many of us out speaking at a variety of professional groups talking about GDUFA. And we have committed to having quarterly meetings with the board of directors of GPhA. Dr. Woodcock has attended every single one of them. We have actually scheduled these around her calendar, again demonstrating the commitment from the agency for making sure that this program is successful.

[OGD Acting Deputy Director of Science] Rob Lionberger walked you through a considerable amount of the accomplishments from the **regulatory science program**. The one thing I would like to point out is that there was about 20 million dollars spent on this program last year. In the previous year, it was probably to the tune of three to four million dollars. And that is a substantial lift for a program. If anybody knows anything about contracts in the federal government system – which is an onerous process – that is a substantial accomplishment.

There was a **Part 15 meeting** [on FY 2014 GDUFA regulatory research priorities] that Rob did with a spectacular job with his staff – they rose to the occasion and basically led the way for what is the expectation for OGD and GDUFA. And they published the **list of FY2014 regulatory research priorities** as required before the end of FY2013.

And in addition to all this stuff we did about GDUFA, we still did our **day-to-day work**. We approved over 425 applications. That is less than what we approved the prior year, but it is much less of a hit than I expected considering the impact of new hires and training new hires. I think that most of you know that your productivity takes a hit when you get a whole lot of new people. But the flip side of that is that we approved many more prior-approval supplements than we did the previous year, and we issued pretty much the same amount of TAs as we had the year before GDUFA.

And we issued a whole bunch of other guidances. There were over 60 new bioequivalence guidances, 40 revised bioequivalence guidances, and there was the stability guidance and accompanying Q&A. None of these were required by GDUFA. This was other work that was done in addition to establishing this program.

### OGD Priorities

I just want to walk through a little bit of what are our priorities at OGD…. Number one priority is GDUFA. Number two priority is GDUFA. What do you think the number three priority is? GDUFA.

At one of our all-hands meetings I made sure to let every single employee in OGD know that these were our priorities, because I had heard that people were not really sure what our priorities were. I think everybody knows what our priority is. I say this, not really tongue-in-cheek because it really is a trueism: People say they dream in color. I dream in GDUFA. There is no doubt about it.

As Dr. Woodcock said yesterday, there are **major reorganizations** underway. There is the OPQ [Office of Pharmaceutical Quality] reorganization, which will consolidate all of the CMC and micro functions for the entire center under one office. So those functions, the disciplines that exist currently in OGD – the chemistry divisions, the DMF group and the micro group – they will move to OPQ.

And then OGD is being reorganized into a separate **super office** in CDER, putting us on parity with the other super offices of other user fee programs – parity with the new drug side. This is what… is on our website: It is part of the minutes of one of our quarterly meetings with the GPhA board of directors ([link provided above](#)).

This is what is proposed for the reorganization structure for OGD: We will have an **office of research and standards**. This is a direct reflection of the fact that GDUFA has a regulatory science program with money and deliverables. This is the only user fee program that has a regulatory science component. I acknowledge those of you who were at the table doing negotiations. It is an exceptional feat to have this as part of GDUFA.

We will have an **office of bioequivalence** with three divisions of bioequivalence, enhancing our bioequivalence staff, and then a division of clinical review – more clinical presence in the Office of Generic Drugs.

When I first joined the agency there was no **medical officer** in OGD. Several years ago there was one medical officer in OGD. And now I think we are approaching ten. In a very short period of time we will have as substantial number of clinicians in OGD.
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We will have an **office of policy**. Dr. Woodcock has a very strong feeling about the need for all offices to have dedicated staff working on policy projects and initiatives, guidances, MAPPs, and that kind of stuff. It is obviously imperative that OGD has its own policy shop because of the regulatory and legal implications of Hatch-Waxman.

And then we will have an **office of regulatory operations**, which will include: ● a division of project management ● a division for labeling review ● a division of filing review, and ● a division of quality management systems. And in our immediate office we will have a clinical safety surveillance staff, [reflecting] the concept of the importance of a clinical interface related to generic drugs. [We will have] an admin staff, and also a communications staff, which we do not have, which is imperative. You will hear more about what we are thinking about our communications staff sometime in the near future.

**OGD Challenges**

Here is a very quick summary of some of the challenges that we have this year:

We have to implement GDUFA. That is a huge lift. It is a monumental task. It is transformational change. This is huge, there is no doubt about it.

We have to **hire**. That is a great thing to be able to do. There are tons of unfunded mandates that come to the agency. But to be able to hire new people to do the work is wonderful. But it is challenging, we all know that. There is an incredible amount of time conducting interviews, selecting candidates, and then the harder part of training those people and getting them up to speed quickly, especially under a new user fee program. Then we have to identify some of the key leadership that is going to fill some of those positions that you saw in the proposed reorganization chart.

Then we have huge **budget changes**. The office went from a total budget of, I am not going to get this straight, from a $5 million operating budget to over or close to $30 million. That is a very substantial change with a small administrative staff. And when you hire people you have to have a place to put them, so there are challenges associated with that.

And on top of all that, we are **moving to White Oak**. We are moving to White Oak next year, sometime in the spring or summer, and there is a phenomenal amount of angst among the staff about moving to White Oak. This will be my third move to White Oak. I tell them, 'I am still alive. I survived it. And I survived it so much that I want to do it again. It is not the end of the world.' As a matter of fact, it will be exceptionally beneficial to OGD to have us at White Oak, where all the other components of the generic drug program are. This will be very good for us.

I want to very briefly highlight our **hires from year one**. We had over 100 new hires just in OGD alone. But the major focus was to bring in CMC reviewers. It was reviewers with expertise in formulation, process, and manufacturing science.

We have a huge number of hires for this fiscal year. We are having a virtual hiring event on November 4. We are shamelessly hiring from all sources. We will take your best people and I am happy to do that. And I will be saying the exact same thing at a CDER all-hands meeting as well. I have not reached out to one person to steal them from somebody, but we have recruited some phenomenal staff to our office. I have emails, CVs, sent to me almost daily. We have some spectacular hires….

Granted there are other components of the agency that are hiring under GDUFA: ● compliance, ● OPQ, and ● ORA. Quite frankly, I am going to be a little selfish – this is all about OGD. We are hiring….

I would just like to close by making this really personal. Why do we have to get this right? Why do we have to do this? And this is why: These are the people who need the medications that you provide. These are the people who use the medications. If we do not get it right, that is who suffers.

I really want to stress that this is a **shared responsibility**. We have to have a shared sense of urgency. The clock is ticking. Keith Flanagan has a whiteboard by his door that he updates every day for how many days there are until cohort three, because that is when the clock really starts clicking. We have a shared sense of ownership for this program. We are accountable for this program collectively and I am hoping that we have a shared commitment to make this a successful program.
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ABSTRACT SUBMISSION DEADLINE:
November 22, 2013 for oral presentation
January 17, 2014 for poster presentation
Interactions Between OGD’s Inactive Ingredients Database Working Group and IPEC on IID Content and Functionality Bearing Fruit

The cooperative effort between FDA’s Inactive Ingredients Database (IID) Working Group and the International Pharmaceutical Excipients Council (IPEC) to improve the IID’s content and functionality is beginning to bear fruit and will gain further momentum from the extra resources that will become available to the Office of Generic Drugs (OGD) to support projects that meet the Generic Drug User Fee Act (GDUFA) goals of creating a more efficient review process.

Facets of the IID initiative that are now gelling include:

- a frequently asked questions (FAQ) that will help clarify the database’s use and a number of areas that have created confusion within the industry regarding FDA’s expectations for how IID references are to be made and supported
- a standardized approach for supplying information to streamline the submission and review processes
- posting historical files on a quarterly basis to allow searches for name or level changes that occurred.
- a review of priority excipient families, including hypromellose, polyethylene oxides, silicone, and carboxomers, and
- a prototype database that explores how data could be more effectively added and accessed

Discussions are also advancing regarding:

- systems for controlling changes made to the IID and communicating them externally and internally
- adding and searching synonyms and trade names, and
- refining the excipient family approach to facilitate common pharm-tox evaluations.

In the longer term, the OGD/IPEC dialogue on the IID, in conjunction with the ongoing effort under GDUFA to create a more efficient drug master file (DMF) system, could open the door for developing a less-cumbersome clearance process for novel excipients – an objective of IPEC’s since its formation two decades ago.

Advancing Communications Include FAQ

At the GPhA Fall Technical Conference in late October in Bethesda, Maryland, OGD Chemistry Division Director Robert Iser reviewed the progress that the OGD working group (WG) and IPEC have made in upgrading the IID and the communication process that supports it.

“I think we have accomplished a lot of good things in terms of working with not only the IPEC working group but also internally,” Iser said.

In an interview with IPQ conducted following Iser’s presentation, Colorcon Global Regulatory Affairs Director David Schoneker, who has been a key player on the IPEC team interacting with OGD’s IID WG, provided further insights on the IPEC/OGD collaboration.

Schoneker shed additional light, in particular, on the discussions underway to simplify the excipient pharm-tox evaluation, submission and review processes when the use of an excipient may not be covered by the levels that already exist in the IID.

The collaboration “has been one of the most valuable interactions that IPEC has ever had with the agency,” he commented, characterizing the discussions as “very open and productive.”

The first FAQ document developed between the IID WG and IPEC has been completed and is currently in FDA’s internal review and approval process, with the expectation that it will be forthcoming soon.

In focus in the initial FAQ is the information that could be submitted for justification of an excipient in an ANDA, how to submit the information to FDA, and how the database will be updated when a new use of an existing excipient or a new excipient is approved in a drug application. Other common industry concerns that will be addressed include nomenclature from the Substance Registration System (SRS), potency listing for families of related excipients, unique ingredient identifier (UNII) codes, and how to address the maximum daily intake of an excipient in ANDA filings.

A second FAQ is planned to address more complicated questions that will require further agency deliberation to answer.

Standardized Pharm-Tox Approaches Sought

Iser discussed the benefits of submitting data in a standardized fashion in general terms and the implications for smoothing work processes and eventually allowing for a more automated population of the IID. [Editor’s Note: Iser’s complete remarks at the GPhA conference are provided below].

In the interview with IPQ, Schoneker focused on IPEC’s...
efforts to come up with a standardized approach for the submission of pharm-tox data, in particular.

IPEC has put together a draft form for pharm-tox data submission that includes fields for toxicology data with supporting regulatory references from other countries. The form could serve as a standard summary document for FDA.

The summary, Schoneker explained, would be submitted in addition to the detailed safety data. The agency could then “determine how much detail they may need for the pharm-tox assessment from those hundreds of pages of tox data as opposed to looking at the summary information, which will provide key outcomes from the studies and other regulatory reviews done around the world.”

Having a standardized, clearly-defined submission template would serve as a guide for companies on what to submit, and aid agency reviewers, who currently receive varying amounts and types of information in a variety of formats.

Although not all information in the template would apply to every submission, the fields could also serve as placeholders for the applicant to explain to agency reviewers why a particular piece of information is not needed.

Once the template is finalized, IPEC’s hope is that it would be made available on the FDA website for anyone to use.

Pharm-tox information was submitted by IPEC to the agency on an initial set of priority excipients that have a number of related grades in the family (hypromellose and polyethylene oxides) prior to the completion of the template. However, the template has been used to submit the data on silicones and carbomers “as examples to show them what we think could be done,” Schoneker explained.

Family Approach Decreases Workload

Grouping excipients into families of related grades to facilitate common pharm-tox study evaluations, as has been done with many of the same ingredients used in the food industry, would decrease data requirements and review time. However, safety and efficacy concerns must be addressed up front for this approach to be viable in the pharmaceutical context.

Under examination by IPEC is the feasibility of using pharm-tox study data performed for a family of excipients to justify the use of different grades within that family – ultimately using one level per family for a specific route of administration. The goal is to eventually build this type of evaluation into the IID. However, initially this assessment and information will be added to the FDA’s website outside of the IID database in a format which will facilitate review by both industry and FDA reviewers.

A key part of the evaluation of the family approach will be ensuring that the different grades do not have an impact on safety when used at different levels in the dosage form.

Schoneker explained that IPEC has already provided summary and detailed safety information to FDA on the four “priority” excipient families in the form of a spreadsheet that includes: ● all of the current IID information for the different dosage forms ● routes of administration and their current listings, and ● the maximum level from a prior precendence of use of one of the grades that the available safety data indicates can be used for each route of administration. The supporting safety data and literature references were also submitted.

To support the maximum level of administration, IPEC “supplied all of the safety information that usually supports much higher levels of use than has been previously listed in the IID since many of these excipients have been used for years as approved food additives, cosmetic ingredients or in other related applications,” Schoneker noted.

The tox and other data was put together from IPEC member companies including Dow, Ashland, Dow-Corning, and Lubrizol, which manufacture the priority ingredients.

Spreadsheets with the data were provided to FDA. When the information was not in the public domain, the data was provided confidentially from the company. “Basically, between us,” Schoneker commented, “we supplied them with all of the safety information needed to support a whole family of grades.”

IPEC’s task is to prove to FDA that specific toxicology study data is not needed for each grade of an excipient, but that extrapolation techniques such as bracketing by key attributes can be used to apply safety information across families and grades.

An example of a family of related grades is the different substitution types of hypromellose which also have many different viscosity grades. The same safety information that exists for certain grades in the family can be used to cover all grades in the family, and this is common for many polymers in particular.

“That is how safety assessment has been done in the food additive arena for years, and most of these excipients are already approved food additives,” Schoneker noted. “No one typically runs toxicology studies on each grade of an excipient in a family and these types of studies will almost never be run since this would simply create redundant data which would have no value.”

The next step in the process will be getting agreement by FDA reviewers that the proposed highest use levels determined by the IPEC committee are valid.
“We are not proposing anything that does not already have a precedence of use,” Schoneker noted. “We are basically saying that the highest level for oral, for instance, that has been used in the IID in the past one of the grades, ought to cover all of the grades, which historically is kind of what FDA did until recently anyway.”

If an agreement is reached, a firm could refer to the “highest level” number for the particular route of administration for all the grades. The aim is to eventually build those numbers into the IID.

Schoneker noted that the association has submitted a list of ten more excipient families that it feels should be worked on after the work on the four priority excipients is completed.

IIG Renamed IID After Going Electronic

During a session on the IID at the IPEC/ExcipientFest conference in May in Baltimore, Maryland, OGD Supervisor Chemist Naiqi Ya provided an update on the progress of the IPEC/OGD IID committee on which he serves. Ya addressed some issues that were not covered in detail by ISER at the GPhA fall conference including: ● IID’s name and which excipients are included ● ownership of the database and who populates it, and ● the issues around determining maximum daily intake (MDI).

The IID was formerly named the inactive ingredient guide, or IIG, when the system was in use in hard copy, Ya explained.

Once the data was migrated to an electronic database format and posted to the agency’s website, the name changed to the Inactive Ingredient Database or IID. He noted that the terms are still used interchangeably in his office and occasionally in OGD presentations.

The format and interface remains the same as in the paper version – a situation that Ya characterized as “not acceptable,” given the flexibility that the electronic format provides in how the data may be presented and searched.

Regarding the contents of the IID, Ya clarified that only inactive ingredients in final dosage forms approved in the United States are in the database. Excipients used elsewhere are not listed.

IID Population and Ownership at Issue

Although OGD populates the IID, it is not the only group that does, and it does not have ownership over the database. Much of the nomenclature work takes place within FDA’s “substance registration system” (SRS), which lists all substances approved for use in drugs, biologics, foods, cosmetics, and devices.

The SRS – jointly owned and administered by FDA and USP – uses the unique ingredient identifier for categorizing substances. The UNII is a “unique, unambiguous, non-semantic, alphanumeric identifier based on a substance’s molecular structure and/or descriptive information,” according to the agency website. Ya noted that OGD is also moving toward using the UNII instead of common or trade names.

Name changes made in the SRS feed into the IID, and OGD is not always aware of the changes before they are made.

Ya cited an example where his office was contacted by industry asking why a particular excipient no longer appeared in the IID.

“No, we did not even notice because we were not looking that closely,” he commented. “Suddenly, we got a lot of phone calls and emails asking us about what happened. We found out that the way things were named had changed in the system.”

Better understanding how the naming process works and improving communication with the SRS team is one of the issues being addressed by the IPEC/OGD IID committee.

During the Q&A after Ya’s presentation, USP Excipients Senior Director Catherine Sheehan supported the OGD effort to move toward using the UNII in the IID.

“From the perspective of the pharmacopeia,” Sheehan commented, “we look at the IID in terms of, first and foremost, the nomenclature. So I am delighted to see that there is an effort to delineate between the different types of naming conventions – the trade names, the synonyms, and the real name – because that is a challenge when we are doing new monograph development or doing modernization or even harmonization. It impacts the compendium in many different aspects.”

Maximum Daily Intake Can Be Calculated

While the intake of excipients in the IID is expressed in terms of potency per dose, two of the “most frequent” questions OGD gets are how to adjust levels based on maximum daily intake (MDI) and the meaning of “per dose.”

Schoneker explained that “confusion has existed in the industry for years about what the potency level actually represents that is listed. It is important to stress that the listed IID potency level is the maximum amount of an excipient that has been approved in one dosage form for a particular route of administration. It is not related to the maximum daily intake unless the approved use that triggered that particular listing in the IID came from a dosage form that was only dosed once per day.”

Ya commented that critical to the ability of a firm or
OGD to calculate the MDI is knowing how many capsules or tablets are taken by a patient each day. Although that information should be included on the drug product label, that is not always the case.

When the information is not on the label, “depending on whom you talk to, they will give you different numbers,” Ya emphasized. “So, internally, we have a challenge about what number we should use as well.”

Once the maximum number of capsules or tablets is known, the MDI can be calculated. Ya noted that if multiple strengths are involved, OGD’s recommendation is to use the lowest strength for the calculation.

At the GPhA conference, OGD’s Iser fielded a question during the Q&A asking for clarification on the calculation of MDI using lower strengths.

“Why should the MDI be calculated on a low strength when that would not reflect actual practice?” an attendee asked. “For example, it would be highly unusual for one to take 30 one mg tablets vs. three 10mg tablets.”

Iser commented that OGD generally takes “the conservative approach of looking at what the likely largest amount is that is practically going to be dosed in a clinical setting or in a pharmacy or hospital. We realize that there are cases where if you take the lowest strength, that is not going to be practical.”

He added that the agency would “welcome discussion” on the approach, as it needs to “come to some agreement on how we deal with maximum daily dose questions, especially...for those products that have labels that do not have a maximum daily dose. As we go through this process we will definitely have more interaction on how to calculate a maximum daily dose.”

Also brought up during the Q&A was the possibility of a system that would allow sponsors to populate the IID database.

Iser commented that the agency would consider such an approach, adding that it would like for the population of all of its databases to become more automated and timely.

**IPEC/IID Meeting Minutes Provide Value**

During the Q&A after Ya’s presentation at the IPEC/ExcipientFest conference, IPEC/OGD IID committee member Schoneker commented on the value of the IPEC/WG meeting minutes and the use of controlled correspondence.

“The link to the meeting minutes is being used by hundreds of companies all over the world, almost as a guidance document,” he pointed out (link provided below). “There is a wealth of information in there – really detailed discussion information and all the outcomes of every single meeting since December 2011.”

“Many companies are using information from these minutes that talks about what you should use as references to set up how to go to OGD and justify certain materials,” Schoneker explained. “It gives detailed information about when you might need tox study data and how to reference drug master files. If you have not been to the FDA website where these minutes are posted, I strongly suggest that you go.”

He emphasized that “the great thing about the relationship that we have been able to build is that IPEC drafts the minutes after the meeting, and then they go to FDA – to the appropriate point person – to make sure that FDA is in agreement with all the points of the minutes. Then FDA posts them on the OGD website. Personally, I do not know of any other industry/FDA interaction that has happened that has been this collaborative with the agency in a way that is really getting information out there quickly which can help during generic drug development. I just wanted to tout how great it is that FDA posts those minutes and how helpful it is to the generic drug industry and to excipient companies as well.”

Regarding the use of controlled correspondence, Schoneker commented that “in the past, the controlled correspondence was really focused on the users asking questions about specific drug applications that were already in process or in the works.”

FDA, he said, “opened that up somewhat during our discussions and defined it with more detail on their website. Now even excipient makers can use the controlled correspondence mechanism as well, as long as they ask questions in the right way. You cannot ask open-ended questions – for example, what is the maximum daily intake limit for X excipient? FDA is not going to be able to give you that because this information is not something that FDA can easily determine at this time. But if you give them some specifics about what you would like to have assessed” – for example, asking if a particular daily intake level needed for a proposed drug application is under a prior precedence of use level for a particular route of administration – “they will typically be able to give you that.”

However, Schoneker clarified later to IPQ, “it may take some time for FDA to be able to do this type of assessment since they cannot currently simply look this up in a database somewhere. This question can only be answered by FDA after doing a fair amount of manual research through old paper and electronic NDAs and ANDAs to find out what the MDIs may have been in these applications.

**DOWNLOADS FROM THE STORY:**
- OGD website
- IPEC/IID working group meeting minutes
OGD’S ROBERT ISER ON THE INACTIVE INGREDIENTS DATABASE

At the GPhA Fall Technical Conference in late October in Bethesda, Maryland, OGD Chemistry Division Director Robert Iser reviewed the progress that the OGD working group (WG) and IPEC have made in upgrading the inactive ingredients database (IID) and the communication process that supports it. He discussed:

- the current IID
- IPEC/IID working group efforts
- a prototype database being developed
- stakeholder interactions, and
- issues and progress.

I am going to go briefly into the IID and what it is. I will also talk a little bit about what the process is and where we have opportunities in that process, and where we have already taken opportunities to enhance communication, to put some fixes in for problems that have historically occurred and to move forward on how we are going to build a better IID for you, the stakeholder users, but also for internal stakeholders.

I am going to talk a little bit about the IID working group, and also about a prototype IID database that we are playing around with internally that may be used to kind of set the stage for how we envision the future database.

The [prototype] was actually presented, I believe, at the AAPS annual meeting last year. There was a poster that kind of gave a lot of details about what we are looking into in terms of enhancing the IID for better use and for more functionality.

Then I will talk about some of the interactions we have had with stakeholders. We have had regular meetings with a working group from IPEC. We have also had a lot of good interactions from other stakeholders both internally and externally in terms of what sorts of things they would like to see in an enhanced IID and how we can go forward in making this whole process better.

I will talk a little bit about how we identified issues, the progress that we made, and then a summary and some resources that are available to you.

**Inactive Ingredients Database**

The inactive ingredients database is basically a list of approved inactive ingredients. You can query it by dosage form, route of administration and those types of things, and you can run reports. Basically it is the highest level approved for a specific route of administration per unit. I know that lots of people have had questions about that…. That is the way it is built right now. It is not the most functional way it could be built – especially moving forward – but that is what we have right at the moment.

Only inactive ingredients in the **final dosage forms** of drug products are in the database. Those are for approved products. Once an inactive ingredient has appeared, it is not considered new, and it may require a less extensive review in many cases. However, if you are using it outside of an approved range or for a different route of administration, then we may need additional information.

This is a very high level process that will be used for the inactive ingredient database (**see box below**).

And as I mentioned before, there are a lot of opportunities at each of these steps. I am going to take a few minutes to walk through these. Actually there should be another box above this that says, ‘we have the submitted NDAs or ANDAs.’ So we have an NDA or ANDA submitted with a list of excipients or inactive ingredients in the formulation saying, ‘we would like to get this product approved. Here is our formulation. Here is the list of excipients that we are going to use.’

Could we do that better? Well, we could have common ways of presenting that information to the FDA. We could have
common ways to review that information. We could have better ways for how we review and capture that information. Could we then populate the database better with that sort of information? There are opportunities there. We are working on one: Can we enhance the data submission standards so that we can get that data in a much easier fashion so that we can populate these databases that everyone uses?

Then we have the FDA drug product database. That is something that captures all of this information for every application that is submitted – whether it is an NDA or ANDA, whether approved or not approved, whether withdrawn or reformulated. All of that information is captured in this huge database, which is also being enhanced. Under a lot of the commitments in GDUFA, we are taking a lot of those resources and seeing what sort of infrastructure, what sort of IT needs do we have, and what we need to enhance. This is one of those things that I think will fall under all those types of commitments. Some are part of the ‘product quality enhancements,’ some are part of the IT needs. So we are going to wrap all that up into enhancements that we can make in the IID and the IID process.

In between the approved application and the database, it says in that yellow box, ‘entering drug product information manually.’ I think everyone in here can see where that could be a problem. Historically that is how it has been done. But if we can get common standards – common data submission standards and expectations out there for the industry and to be used internally – can we do more in an automated fashion? Of course we can. That is an area we are working on right now with folks in the several of the offices in CDER – the business informatics folks, the strategic planning folks – so that we can get that information into the database better.

Then we generate the list of inactive ingredients. We have a huge list of inactive ingredients, and it has to be filtered to go into the IID. So we have opportunities here: Are there duplications? What is the highest level for this route of administration? Can we format that whole process, that whole database better? And I would say yes, we can.

We are talking about how best to format it. You will see in the prototype that I talk about that we have some ideas. We have shared those ideas with folks who are looking at building not only the drug product database where we would store all this data, but also the outputs of that database, so that it is better, easier to use, and more functional for the industry and for us.

There is a box there that says, ‘FDA substance registration system’ – the SRS system. That is where a lot of the naming and nomenclature work occurs. That feeds into the inactive ingredient database too. If names change there, that also changes the IID, which then may cause there to be level changes. So that is one of the issues that we will talk about that we are trying to resolve – how to have a better way of finding out what has changed, what kind of change occurred before it happened, and what the synonyms of that change are. Historically, we can go back and say, ‘well this is exactly the same as that ingredient that was already in there. It is not really a change in the ingredient. It is just a change in the name.’

The other yellow box there is for querying the inactive ingredient on the highest level for a particular dosage form or route of administration. Can we build it to be better, in terms of not only the query functions, but also for the information that is available? It was mentioned that we could have maximum daily dose, and maximum daily intake built into the databases, and that would be great. We will talk a little bit about that.

It is a very labor-intensive state that we are in because of the fact that we build all of these based on the approved labels. As everyone in here knows, those approved labels look very different between different drugs, different types of drugs, different indications, different routes of administration, and different populations. It makes it very difficult to populate a database with ‘this is the maximum daily intake of this ingredient for this route of administration always.’ It is very difficult. But we will work through that. We hope to enhance the way we build our database to put those types of functionalities in.

**IID Working Group**

We had a lot of concerns and needs when it came to the database, so we built a working group, which the government does typically. This working group has worked extremely hard since 2011. I am on this working group. [OGD Regulatory Support Manager Iain Margand] and [OGD Regulatory Health Project Manager Johnny Young], who spoke earlier, are also on the working group….
I like to say that this is kind of our hobby, but many times it is not. It becomes something that is very labor-intensive, and we realize that there is a lot of dependency, both externally and internally, on this database. So we take it very seriously when we have people coming in with concerns on the data that are available.

The working group is cross-disciplinary with membership throughout OGD, including from chemistry, bio-equivalence, the clinical review side, the regulatory support branch, media office, and the Orange Book staff.

One goal when we started this working group was to see if we could find some way to communicate with all the people that are involved in putting the data into the database, to standardize it, and to ensure that the data in the IID is accurate and complete.

I do not know if anyone has counted recently, but there are about 12,000 entries in the inactive ingredients database. Behind that are tens of thousands of ingredients for all approved ANDAs and NDAs. That is a pretty large amount of data that has been sitting there informing both the industry and the FDA in terms of approved excipients. It is a major task to go through that data to make sure that it is accurate and complete. We do have efforts underway to look at both of those.

Another goal of the working group was to improve the database usability. We talked about that a little bit already. Can we build more functionality into the query functions? Can we build maximum daily intake into the database? Can we be better at linking some of the naming so things are easier to find – ingredients that may or may not be clearly stated as to what they are? Can we have some change history? Can we have all of those types of things? We are looking into many of those things and we will talk about those as we go through some of the issues and some of the progress that we have made.

The working group wanted to survey not only the industry, but also the internal users on what our needs are. We worked with IPEC to get an idea of what sorts of priorities there are in terms of excipients. And we also talked to other people throughout the office and the other users in CDER to look at what the needs are for this sort of database – how we can do it better and how we can present it in a much more functional way.

So, a little naively, we put this working group together in 2011, and said, ‘oh yeah, we can start working on this and we will just deal with the really high level topics. We will make sure the data is clean. We will have some ideas of how to make it functional. We will get some ideas of what the priorities are. And within a couple of years we will be down the road a lot further.’ But it became very clear that the roles of this working group and this now-expanded program of the IID are much larger, as you can guess, than what we thought naively at the beginning.

I have a circular chart or picture of what the roles of this working group have morphed into (see box at right).

We will just start, in no particular order: Responding to technical queries. We have lots of people that come in and say, ‘the level is wrong’ or ‘the excipient is not there. I know it was approved, why is it not there?’ And we take those types of things very seriously. But there is also a process we have to go through to get that information so that we can inform the folks who are building the database on how to put that information in.

It takes time, because we do not have a designated group that is doing a lot of these functions. It is kind of being built as we go. We are going to have more resources available to do this now because of the fact that we have GDUFA and this fits into a lot of those commitments.

But when we started this group back in 2011, we also started getting a lot queries. We said, ‘okay we need to spend some time, and we need people involved, to say we need resources to respond to these queries.’ They are very important, because if there is something that is not there and you know it should be, we need to know that and we need to be able to fix that information.
Tied to that is doing some sort of **quality control** on the current data and the new data that is going in. There are new databases that are being built, new systems that are being built throughout CDER, that are addressing this from the quality control side – looking at data and getting people involved if there needs to be some subject matter expert to see if something is correct before it is entered – to QC that new data so that the IID is populated with data that is correct, complete, accurate, and usable to you.

**Communicating with stakeholders:** What I am doing today is part of that function. We have also had other opportunities to talk to people at other workshops. As I mentioned, we have been having regular meetings with an IPEC working group that includes some representation from GPhA at some of those meetings to talk about what the issues are. What sorts of things can we address? What are the sorts of things we may or may not be able to address? And then we make a list of those and prioritize them so we can work all this into our vision for this new inactive ingredients database.

As part of our review function, and the technical review function, we also **evaluate the use** of the excipients. Many times there are questions about, ‘can we use this excipient at this level?’ It might include our working group, it might not. There may be times when folks who are doing the technical review – whether it be in the division of bioequivalence or chemistry – say, ‘is this level acceptable based on what is in the IID?’ We may have to get involved in that.

Part of the process includes evaluating use – SAE [safety and efficacy]. We are talking about how we can also do that better. How can we group some of this information together to get a better way of presenting it based on qualified safety data and present that to the industry and to internal users so that we can make a better determination of whether an excipient is safe for use in a particular product?

I put on the slide ‘**develop and maintain the database.**’ We put that in there, but it turns out that is probably not going to be as much our function as it is going to be the people who typically do that – the database folks, the folks who are in the business informatics side who are building the database and maintaining it. But we will be able to inform that process as the subject matter experts and suggest the way it should be designed so it is better for the users.

You can see in this circular loop of all the roles that this working group has kind of taken on over the course of the last few years. All of them are linked together. All of them have a lot to do with what we are talking about today.

A little bit about the **standardization of ingredient names.** The working group has had multiple meetings with the substance registration system database folks – the people who man and manage the SRS database. We are looking for whether can we better include not only the name that is recommended, but also any synonyms or generic names or compendial names or brand names so it is easier to find those types of listings in the IID.

We have talked about improving the usability of the IID. There is a lot of demand for its use. We had lots of people calling us when it was down last week. There is historical data that is available, but it is not as easy to use because it is just a list of excipients. It is much easier to query the current IID to get the information. We are both very dependent on this to make decisions – not only you for how you formulate your products, but also from our end in making decisions on the acceptability of the use of the excipients.

**IID Prototype Database**

We are developing a prototype IID database internally to get an idea of what we would like to see. We shared that database and all of the fields that are in that prototype database with the business informatics office so that they can see if maybe we can build this into the enhanced future IID so that it could have a more searchable, user-friendly interface.

We have a maximum daily intake. Here is a calculation of maximum daily intake – the MDD [maximum daily dose] divided by the amount of the drug per unit, multiplied by the potency of the inactive ingredient for the dosage form. We talked about this in more detail with regard to how we can integrate this sort of information into a prototype database. I have a reference for a poster that was presented on the prototype at AAPS.

It was really rough. From our end, we, as chemists, put this database together as we would like to see it. But that is
not necessarily the best design for the internal users at FDA or the external users. At least it gives a road map or idea of what sorts of things we would like to see in the database and what you would like to see based on the feedback we have gotten from the industry.

We have developed the prototype database, and this is what the OGD interface would look like (see box at right).

Maybe in the future it would look like this for the external users, too. You would input an inactive ingredient that you can search for. You could search for route of administration or dosage form. We could search for, internally, the NDA or ANDA. We do not have any intention of putting the approved NDA or ANDA number on the external database....

The prototype [can also create a] report that can capture a maximum internal intake based on the maximum daily dosage.

It all sounds really good. It would be really nice to be able to say that we could have this tomorrow. It is very difficult to capture all the maximum daily dose and daily intake data because of all the complications that I discussed before: ● the population that is going to be used ● what the labeling is going to look like, if there even is a maximum daily dose for that sort of product that happens to be the highest level approved in the IID ● units, and ● the different sorts of routes of administration and dosage form that really complicate the matter.

I think working through this, and engaging not only the industry stakeholders but also the folks internally, we can move further along in having a much more functional database that includes some of this information.

**Stakeholder Interactions**

I did mention several times that we have had regular meetings with IPEC. We have had six meetings with an IPEC working group that is focusing on a lot of the IID questions that have come to them from their customers. We have also had a regular meeting several times throughout the years to discuss not only what those questions are that are coming into them, but also those questions that are coming into us at OGD, and what sorts of things can we do to make this process much better.

[I will discuss] a few of the action items from the first two years, including polling member companies and developing a priority list of excipients that have issues based on recent IID changes. And at that time, recent changes were that the naming was changed or all of a sudden the levels may have changed. It caused real problems with people being able to find accurate information for the approved level for that ingredient.

We have been working through the development of an FAQ document, which we will talk a little bit about in a later slide.

**Posting historical IID files** on a quarterly basis: We have those now up on the IID website. These are the historical data, so you can go back and find out if a name has changed or if some level has changed. It is not as easy as we would like it to be.

In the future, we would like to have some change control using change management approaches so that we can actually report what types of changes have occurred on the website to make it easier for people to see what has been
changed. We are working on that. We do not have that functionality on the web as we speak.

As we talked about also, we are exploring adding **synonyms and trade names** to make it is easier to find things, easier to map to the various excipients and levels.

We have had **additional meetings**, regular meetings to discuss how best to move forward. It is nice to have interactions with the users and the people who are dealing with a lot of these issues and the manufacturers of excipients, and how they are dealing with queries from the FDA, and also from the industry stakeholders that inform this whole process.

We created a **list of priority ingredients together with IPEC**. A lot of the information that I am pulling from here is on the OGD website. We do post the minutes of the meetings. We post some of the information on the priority excipients that we have been working on, the progress we have made to-date, and some of the discussions we have had on the FAQ document. That information has been posted on the OGD website since the first 2011 meeting with the IPEC working group ([link provided above](#)).

The priority list of excipients include hypromellose, polyethylene oxides, silicone, and carbomers. We are looking at an approach to how best to take **groups of excipients** that are commonly used and present those in a way that we can take an acceptable global or family pharm-tox study that was done and completed, and look at whether we could use that study to justify the use of different grades of a certain family of excipients – if we know that those grades do not really matter in terms of safety.

We are working on putting together a spreadsheet type of approach. You will see some **prototypes** of that. Those are not all final and most of the information is redacted from those that are on the web. But they give you an idea of the thought-processes: Can we group these things into families based on a pharm-tox study that is out there and use one level to justify the use of all of those in a specific route of administration? It is an interesting concept.

We are also working through the clinical review branch, which is looking at this from the pharm-tox side and also from the efficacy side: Will this have an impact on efficacy in terms of use of these excipients at certain levels in a certain dosage form?

Hopefully, if we can get something like this built either as an addendum to the IID or just built into the IID itself, it should expedite the review and make it much more user-friendly in the future both externally and internally. Hopefully, the final conclusions of this will either be posted on the FDA website, related to the IID, or built into the system itself.

But we are going to have to talk about how to present this information – how to move forward with this information and make sure that we communicate it internally and externally so that we can use it in the best way we can. We do not want people taking this data and saying, ‘well, it is generally acceptable.’ We want to make sure that we are very clear regarding how this data should be used. So stay tuned. We are not there yet. We have some trial balloons of excipients that are on the priority list that we are trying out.

OGD has completed most of the work on the hypromellose review and is working with IPEC to develop a table/template similar to the agency’s current pharm-tox table that could be used to expedite review/use in the future. The final conclusions will likely be posted on the FDA website.

We also are developing an **FAQ document** through our discussions with IPEC and internal discussions about what sorts of common questions are being asked of us and from us in terms of what sorts of information could be submitted for justification of an excipient or how you submit the information or what the process is – all of those types of things. It is currently pending our internal review process. So it is moving through the process of how best to communicate this FAQ document. There are some details about how we went about developing this during those discussions we had with IPEC on the OGD website. But this is not a final document. The documents that are on there, hopefully we can move toward completion and get something out there that is a communication tool and answer some of these common questions.
Issues and Progress

One of the other roles that our working group had was updating the IID. As I mentioned before, we have posted four years of historical IID data. That is updated when the IID is updated on a quarterly basis. There is another set of historical data that stays on there. You can pull that data and at least see if there are any changes.

That is not the best system, as I have said before. So we are working on a method of how we can post revisions and what sorts of revisions we can post – whether they will be on the external webpage and how that is going to look, and whether they will be posted prior to being effective, and how that is going to look. We are having those discussions also with the people who are working on developing what our new database will look like.

We know it is something that is needed. In some sort of database like this, we need to be able to communicate changes to the people who are using it – whether it is industry using it to develop the products or internally by our review staff – to be able to see what has changed and to be able to consider that when we are doing our review.

I mentioned also linking to synonyms. I put a link up here to the substance registration system [SRS] where you can put in a query for an ingredient and you will get a list of synonyms. Can we build this sort of functionality directly into the IID in a much easier way? That is something we are also looking into.

I hate to say that we are looking into all of these things. We really do have a list of priorities. One of the priorities is that the data that is currently in there is correct, accurate, and complete. I think that should be our number one priority. We have a list of other priorities – a list of things we would like to see in the new database. We are working through all of those.

There are some inactive ingredient considerations that are in the RTR [refuse to receive] draft guidance – things like what sort of data and what sort of justification should be provided for an inactive ingredient that exceeds the IID limit for the units. It elaborates a little bit more in the guidance that pharm-tox studies should follow the current guidance. There is a mechanism in place to take a look at the pharm-tox studies that may be submitted to allow us to quickly determine if those studies are acceptable or not so we can communicate that back quickly.

We need to talk further about what sources of pharm-tox studies will be permitted. Obviously, we do not just want a journal article. But we may have availability of the data. How do we evaluate that? How do we link that to the ANDA submission that is coming in?

If you have a CDER-approved drug that uses an excipient at a particular level, provide that information to us so we can take a look at that and see if that matches the information we have.

The controlled correspondence procedure…is not the best procedure right at the moment. We have lots of questions and we are dealing with those questions as best we can. We do have metrics on those questions as we move through GDUFA years three, four and five. Hopefully, one way of reducing some of those questions is getting better communications out in terms of some frequently asked questions and a better IID database.

It elaborates a little bit more in the RTR guidance…about what sorts of expectations we have. Specifically for oral liquid drug products, do not use the percentage listed in the IID to calculate the amount delivered per dose per day based on the label of the RLD, and provide that information also for powders and oral suspensions. So do not just rely on the percentage that is in there, because that percentage could be a little misleading in terms of how much of the excipient is actually in the formulation that was approved.

Summary

To summarize, we have a working group that was formed in 2011. Lots of hard work has been put into this working group. I think we have accomplished a lot of good things in terms of working with not only the IPEC working group but also internally, moving through the process of trying to enhance the database and enhance our communication about what is going on with the database.
Developing a prototype, I think, was key to us, even though that prototype may not be the one that will ultimately be used.

We were able to set up a road map for how we would like to build an inactive ingredients database so that we could use it easier and so that you can use it easier in a much more functional way.

Routine stakeholder communication: We have regular meetings with the IPEC working group. But also we are going to have more communications, whether it is at meetings like this or webinars, as we proceed with enhancing the database.

Some of the issues related to the current IID – not as many as we would like, of course – have been identified, such as: ● history ● some of the data that was not there that we have been able to add, and ● some of the information that was inaccurate that we have been able to correct. But we need to do better in terms of communicating those types of changes and having a mechanism to do that internally.

And as mentioned, under GDUFA, my hope, and I think the realization, is that a lot of these IID database revisions and tasks will fit into the ‘efficiency enhancement’ bucket in the GDUFA commitments – the database commitments that we have of enhancing how we put these quality databases together, how we use them, and how we enhance the efficiency of our review processes.

IID questions, specifically, can be submitted through the controlled correspondence mechanisms….
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FDA Moves Quickly to Implement Compounding Provisions of Drug Quality and Security Act

FDA is moving quickly to give regulatory flesh to the compounding provisions of the new Drug Quality and Security Act of 2013 (DQSA), signed into law by President Obama on November 27.

On December 4, a week after the signing, FDA issued three draft guidances and three companion Federal Register (FR) notices related to the implementation of the compounding provisions of the act.

The three draft guidances cover: ● overarching rules for what constitutes pharmacy compounding and how enforcement for violations may be applied ● a definition of a new category of compounder created by the DQSA – “an outsourcing facility” – and the registration requirements, and ● interim requirements for ongoing reporting of information to FDA by the outsourced facilities on their products and services.

The FR notices explain that FDA will be producing listings of bulk drug substances used in pharmacy compounding and products made from those substances as well as a list of “difficult-to-compound” products. The agency is requesting that industry nominate candidates for the lists. Included in the FR notices is the information required for nominations to be considered as well as a template for the submission of candidates for the difficult to compound list.

The 60-day comment period on the three guidances extends until February 3. Comments on the FR notices are due by March 4.

The speed at which the agency is moving in the act’s implementation reflects the central place that compounding operations have occupied on FDA’s inspection and health protection radar screen since the fall 2012 meningitis outbreak caused by fungal-contaminated sterile methylpredione produced by NECC (see IPQ Special Report November, 2012).

Pharmaceutical manufacturers are impacted by what is happening in the compounding arena and should be paying close attention to how the new act is being implemented.

A longstanding issue is the line between compounding and unapproved drugs, which may compete with products that have to meet stringent approval and inspection demands. The drug shortage issue is also at play in that pharmacy compounders step in to fill perceived market gaps – again, often with unclear authority to do so.

The association of pharma products with the quality and public health problems created by compounding pharmacies and other handlers of their products downstream in the distribution chain is also of very real concern to the industry – both in terms of brand-name tarnishing, but also in their potential involvement in recalls and other follow up legal and enforcement actions.

DQSA Clarifies FDA Jurisdiction

The Congressional effort to strengthen and clarify FDA’s regulatory authority in the compounding arena extends back to the 1997 FDA Modernization Act. The compounding provisions of FDAMA, however, ran into court challenges, one of which led to a circuit-court level decision that the advertising restrictions were unconstitutional on free speech grounds and were not separable from the other sections of 503A, rendering 503A as a whole unenforceable (ibid, pp. 30-32).

DQSA removes the advertising-related provisions, restoring the applicability of the rest of 503A to compounders nationwide.

503A describes the conditions under which certain compounded human drug products are entitled to exemptions from three sections of the FDCA requiring: ● compliance with CGMPs ● labeling with adequate directions for use, and ● FDA approval prior to marketing.

The DQSA also creates a new section 503B(b) in the FDCA. Under the new section, a compounder can become an “outsourcing facility,” which carries additional requirements including meeting applicable CGMPs and FDA inspection.

The current legislative effort began with the fall 2012 meningitis outbreak and was further spurred by the findings of serious GMP noncompliance among sterile compounders and tainted products through FDA’s nationwide inspection crackdown since then.

As of April, 2013, FDA had completed inspections of 56 sterile product compounding operations from a blitz that began in February (see IPQ Monthly Update, May 2013, pp. 34-41). Of these, 25 were conducted on a “for cause” basis in response to complaints, and another 31 were proactive inspections of compounders known to have produced sterile drugs in the past. [Editor’s Note: For an in-depth analysis of the results of the first 14 of these inspections, see IPQ Monthly Update, March 2013, pp. 30-34.]

Since April, an additional 20 FDA 483s have been given to pharmacy compounders. The agency has issued four warning letters to compounding operations since the crackdown began.

As of October 23, 2013 – the most recent date for which the Center for Disease Control statistics are available – 751 cases...
of fungal meningitis, stroke believed to be caused by fungal meningitis, or central nervous system infections tied to the tainted NECC drugs had been reported in 19 states, and 64 people had died.

**Enforcement Framework Provided**

The overarching draft guidance, “Pharmacy Compounding of Human Drugs Under Section 503A of the FDCA,” provides FDA’s definitions of what constitutes pharmacy compounding and how it is conducted – for example, that products must be compounded based on an individual prescription and that a licensed pharmacist perform the compounding.

The guidance describes some of the possible enforcement actions FDA may bring against individuals or firms that compound drugs in violation of the law. It also explains how pharmacy compounding is defined and notes what aspects of GMPs apply.

In addition, it rescinds a draft Memorandum of Understanding (MOU) between FDA and the states as required under the 1997 FDAMA regarding pharmacy compounding and interstate distribution of compounded products. The MOU had not been finalized.

The guidance states that a new MOU will be forthcoming for comment. FDA will develop a standard MOU for use between the agency and the States in consultation with the National Association of Boards of Pharmacy (NABP) that “will address the interstate distribution of inordinate amounts of compounded drug products and provide for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside that State.”

Several parts of section 503A require rulemaking and consultation with a Pharmacy Compounding Advisory Committee to implement. The guidance explains how those provisions will be applied pending the consultations and rulemaking.

A facility can qualify for exemptions from the FDA approval requirements in section 505 of the FDCA and the requirement to label products with adequate directions for use by section 502(f)(1) if the requirements in section 503B are met.

FDA anticipates that state boards of pharmacy will continue their oversight and regulation of the practice of pharmacy, including traditional pharmacy compounding. The agency also intends to continue to cooperate with State authorities to address pharmacy compounding activities that may be violative of the FDCA.

**“Outsourcing Facility” Category Created**

Under the new section 503B(b), an outsourcing facility may be able to qualify for exemptions from the FDA approval requirements and the requirement to label products with adequate directions for use, but not for an exemption from CGMP requirements.

The new draft guidance on outsourcing facilities explains that, in addition to complying with CGMPs, they: ● will be inspected by FDA according to a risk-based schedule, and ● must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound.

If compounders register with FDA as outsourcing facilities, hospitals and other health care providers that source from them can be assured that the drugs they provide to their patients were compounded in facilities that are subject to CGMP requirements and federal oversight – an incentive for compounders to register.

If a compounding chooses not to register as an outsourcing facility and qualify for the exemptions under section 503B, the compounding could qualify for the exemptions under section 503A. Otherwise, it would be subject to all of the requirements in the FDCA applicable to conventional manufacturers.

The draft guidance indicates that more directions will be forthcoming from FDA on the CGMP requirements that outsourcing facilities will need to meet.

After the initial registration, a facility that elects to register with FDA as an outsourcing facility must also do so annually. Upon registration, the outsourcing facility must provide its name, place of business, a unique facility identifier, and a point of contact email address. The outsourcing facility must also indicate whether it intends to compound, within the next calendar year, a drug that appears on FDA’s drug shortage list and whether it compounds from bulk drug substances, and, if so, whether it compounds sterile drugs.

**Reporting for Outsourcing Facilities Defined**

The third in the new draft guidance series – covering ongoing reporting for outsourcing facilities – explains that the facility must submit a report to FDA identifying the drugs compounded by the facility during the previous 6-month period upon initial registration, and twice each year afterward.

The guidance provides a template and instructions for submission of the information. The following information must be submitted: ● active ingredient and strength of active ingredient per unit ● source of the active ingredient (bulk or finished drug) ● National Drug Code (NDC) number of the source drug or bulk active ingredient, if available ● dosage form and route of administration ● package description ● number of individual units produced, and ● NDC number of the final product, if assigned.
Help Sought on Bulk Drugs for Compounding

In the first of its December 4 FR notices, FDA announced its withdrawal of a 1999 proposed rule to list bulk drug substances used in pharmacy compounding and its intention to develop a new list as well as a list of the drug products the bulk is used to produce.

To identify candidates for the lists, interested parties may nominate specific bulk drug substances and products. FDA describes in the FR the information that should be provided to the agency in support of each nomination.

After evaluating the nominations and, as required by section 503A, consulting with USP and the Pharmacy Compounding Advisory Committee as required by section 503A, FDA will issue the lists for public comment.

The notice explains what information the nominations should include. If the information requested is unknown or unavailable, that should be noted.

For bulk drug substances: ● ingredient name ● chemical name ● common name ● chemical grade or description of the strength, quality, and purity of the ingredient ● information about how the ingredient is supplied (e.g., powder, liquid) ● information about recognition of the substance in foreign pharmacopeias and the status of its registration(s) in other countries, including whether information has been submitted to USP for consideration of monograph development, and ● a bibliography of available safety and efficacy data, including any relevant peer-reviewed medical literature.

For compounded products that are produced from the bulk drug substance, information regarding the: ● dosage form(s) into which the drug substance will be compounded (including formulations) ● strength(s) of the compounded product(s) ● anticipated route(s) of administration of the compounded product(s) ● past and proposed use(s) of the compounded product(s), including the rationale for its use or why the compounded product(s), as opposed to an FDA-approved product, is necessary, and ● available stability data for the compounded product(s).

A second FR notice provides instructions regarding electronic submission of the requested information.

**What Are “Difficult-to-Compound” Drugs?**

In the third FR notice, FDA announced its intent to develop a list of drug products that present “demonstrable difficulties for compounding” – the so-called “difficult-to-compound list.”

To identify candidates for this list, FDA is encouraging interested groups and individuals to nominate specific drug products or categories of drug products. In the notice it describes what may constitute “difficult-to-compound” products and the information that should be provided to the agency in support of each nomination.

Nominations for each drug product or drug product category should include the reason why the drug product or drug product category should be included on the list, taking into account the risks and benefits to patients.

Reasons may include adverse effects that could result when the drug product is not made according to appropriate conditions and the potential effect of compounding on the potency, purity, and quality, which could affect safety and effectiveness.

Factors that may be relevant to this determination include: ● the drug delivery system ● drug formulation and consistency ● bioavailability ● complexity of compounding ● the degree of sophistication of facilities and equipment needed to compound the drug ● training required, and ● testing and quality assurance requirements.

A link to the March, 1999 rule on drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness was also provided in the same FR as a reference.

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**DOWNLOADS FROM THE STORY:**

FDA draft guidelines
- Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act
- Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act
- Interim Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Federal Register notices:
- List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Request for Nominations
- Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act Concerning Outsourcing Facilities; Request for Nominations
- List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness: Final Rule (1999)
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A Well-Thought-Out Immunogenicity Clinical Evaluation is Needed to Overcome Prediction Limitations for MAbs, NIBSC Expert Cautions

A well-thought-out clinical evaluation of the immunogenicity of monoclonal antibodies is a critical component of the regulatory clearance pathway, and making predictions and generalizations short of this clinical analysis is dangerous, UK’s National Institute for Biological Standards and Control (NIBSC) Biotherapeutics Group Head Robin Thorpe cautioned the attendees at a PDA MAb workshop in Basel, Switzerland in September. The limitations in a MAb sponsor’s ability to make immunogenicity predictions during the product characterization phase of development and the need for carrying out a carefully crafted clinical assessment strategy was a key theme of Thorpe’s during his presentation and in the discussion that followed.

Thorpe’s talk amounted to a valedictory address capping a 30-year career at UK’s NIBSC, where he played a prominent role in advancing biotech regulatory standards and understanding. He retired from NIBSC at the end of October.

The PDA workshop at which Thorpe spoke was focused specifically on the “CMC and regulatory considerations for immunogenicity assessment” of monoclonals. The four sessions of the workshop addressed: ● new guidelines and regulatory considerations ● the relationship of quality attributes to immunogenicity ● analytical requirements and challenges, and ● the implications of immunogenicity on the development of biosimilars.

Preparing the ground for Thorpe at the opening regulatory session was a presentation by an expert on immunogenicity assessments from Austria’s Agency for Health and Food Safety (AGES), Biologics Preclinical Assessment Group Head Gunter Waxenecker. The Austrian official reviewed the current expectations and guidance from European regulators for the clinical assessment process, and the challenges for MAb assessments, in particular.

Assessments Vary Widely But Getting Better

Reiterating the need for carrying out the assessments for each individual product, Thorpe pointed out that “if you actually look at the literature, you will find conflicting reports, quite honestly, for just about any antibody. Sometimes it seems you do get an impairment, and sometimes you don’t,” which is “probably because of the way in which that is being evaluated rather than reality.”

“The unfortunate consequences of that,” he stressed, is that it “makes the prediction of clinical effects of antibody development difficult and, in fact, nearly impossible. Generalizations relating to this are very dangerous. Having said that, generalizations are very often made.”

The problem, Thorpe summarized, is that “it is more or less impossible to predict the things you really want to predict, such as the incidence of immunogenicity, the characteristics of the immune response, and particularly, the clinical consequences of immunogenicity. These have to be assessed in appropriate studies, because you really can’t do much from a predictive point of view.”

The NIBSC official circled back to reemphasize the point at the conclusion of the discussion period that followed his talk at the session.

Thorpe explained that during his tenure at the institute he “looked at quite a lot of immunogenicity studies for marketing authorizations…largely because clinical colleagues weren’t that impressed with what they saw, and they wanted to see whether somebody else from a different background had the same concerns.”

What stuck him is the “enormous” variation in the quality of those studies and the assays they employed “from very good to absolutely appalling.” The assumption that big pharma does these well and small companies with limited resources don’t “is not true,” he noted. “It is very variable. You can’t really predict it.”

Concentrating on producing a good immunogenicity study at the marketing authorization application stage is “extremely important,” the biotech expert said, adding that “obviously, you have to follow up with post-marketing studies as well.”

At the application stage, “you really do need to put in a study that is convincing from all angles – that really shows that you don’t have a problem – or at least that you have identified the potential for a problem and you better look out for it. I think anything else is really just an add-on.”

Thorpe went on to emphasize that “the predictive stuff” he has seen “doesn’t really add much” at that stage “because you are going to have to do the clinical study anyway.”
Referencing an earlier comment by Dutch Medicines Evaluation Board (MEB) Biological Products Assessor Martijn van der Plas, Thorpe maintained that “the real value” of the predictive analytical studies is “in the selection of appropriate products.” He reiterated that it is up to the company as a business risk decision to determine how much effort it wants to put into this type of characterization work.

Van der Plas added to Thorpe’s comment on the wide disparity in the quality of immunogenicity studies by noting that since the coming into effect of the EMA’s immunogenicity guideline “there has been a sort of clean up, and both the immunogenicity assays and other assays and their assessment has significantly improved.”

**MAb Addendum Takes Effect in Late 2012**

Drawing from his extensive experience with biotech products at NIBSC, Thorpe’s presentation encompassed: ● the clinical consequences of immunogenicity ● current EMA guidance and expectations, and ● considerations for biosimilars. *(The presentation is included in full on pp. 36-43.)*

He shared insights into the development of, and key themes in, the current European guidelines related to immunogenicity, which he participated in drafting.

A general guideline on immunogenicity, applicable to all products, was released by Europe’s Committee for Healthcare and Medicinal Products (CHMP) in 2008. Thorpe commented that the guideline was the first regulatory effort to focus specifically on immunogenicity and contains “all sorts of valuable advice.” He added that a redraft is now being planned.

**With Thorpe and AGES’ Waxenecker playing key roles, EMA’s Biologics Working Party (BWP) began the drafting process on an addendum to the general guideline that would address the immunogenicity issues for monoclonal antibodies, in particular. The MAb immunogenicity addendum guideline was completed and came into effect in December of 2012.**

Driving the focus on monoclonal immunogenicity, in particular, was the size of the class and the particular challenges that MAbs pose, such as dealing with the problem of preexisting antibodies and measuring one against another.

The addendum, Thorpe noted, is aimed at products in the final stage of development. It reviews the major quality and clinical considerations relevant to the MAb assessments.

While strategies may vary, the guideline stresses the criticality of having a strategy that allows for discriminating between positive and negative samples and that can determine whether there is any clinical significance.

One of the key challenges is selecting the right type of assay. Thorpe touted the extra power that the electrochemiluminescence (ECL) assay provides and expressed his support for the two-tiered approach that the guidance outlines. The competitive binding assays may be more revealing than biological assays in the monoclonals context, he maintained.

**The MAb immunogenicity addendum proceeds to deal with the clinical aspects and the risk measurement, monitoring, and mitigation called for by this product class.**

Thorpe again cautioned that although monoclonals “are often considered as one group, they are in fact pretty heterogeneous. There are all sorts of factors, which can make trying to make generalizations difficult and dangerous.”

He cited examples of the different responses a particular MAb may have among patients groups with different clinical problems, as well as among different patient groups with the same problem – for example, children vs. adults and immunosuppressed vs. non-immunosuppressed.

**Biosimilars Guideline Weighs In On Challenges of Comparative Immunogenicity**

Also adding to the immunogenicity guidance library in Europe is the biosimilars guideline, which came into effect at the end of 2012 along with the addendum on MAb immunogenicity.

The biosimilars guideline didn’t address immunogenicity in the early drafts “but it does now,” Thorpe commented, “particularly in the clinical aspects.”

Noting the stress placed in the guideline on the importance of carrying out meaningful comparability studies, Thorpe delved into why the “field of comparative immunogenicity...is much more problematic than straightforward immunogenicity of a single product.”

What this is tantamount to is comparing the immunogenicity of effectively different products, “because you don’t know yet whether they are biosimilar,” he pointed out. The consequences of immunogenicity also have to be compared, and the comparison probably has to continue post-approval “simply to build up patient numbers.”

“Comparative immunogenicity is really difficult,” Thorpe
stressed. “It is probably the most difficult thing about the assay side of developing biosimilars.”

The NIBSC expert went on to assess the challenges of this comparative analysis and potential strategies for conducting it.

Although a one-assay strategy is easier, he recommends a two-assay approach as more comprehensive and less risky.

**Clinical Assessment A Biosimilars Weak Spot**

To understand the biosimilar clinical issues regarding immunogenicity, developers of MAb biosimilars need to read the general immunogenicity guideline and the MAb addendum as well as the biosimilar MAb guideline, Thorpe advises.

The biosimilar guideline “does spell this out quite well and clearly, which I think is really needed, because on looking through some of these applications for biosimilar monoclonals, there seems to be a lot to be desired from the immunogenicity point of view. It really does need to be looked at carefully.”

Ignored by some of the applications that Thorpe has seen is that the immunogenicity, or lack thereof, of the marketed innovator product “doesn’t influence the need for comparative immunogenicity studies.”

Even though the marketed G-CSF, for example, has not been immunogenic, a biosimilar has to be treated as a new product and studied accordingly.

“If you are lucky,” the NIBSC expert said, the studies show that the innovator monoclonal and the biosimilar are the same. A second possibility is that the biosimilar shows higher immunogenicity, in which case “you are dead.”

The third outcome is a finding of lower immunogenicity of the biosimilar “which is really good from the clinical point of view.... But of course, the problem from the quality point of view is that there must be some underlying scientific reason for that. And if it is real, then it might be that these products are dissimilar, which is not so good if you are trying to promote this idea of biosimilar.” The latter findings would have to be explained, Thorpe stressed – for example, that the assays are implicated.

Thorpe concluded his presentation by summarizing that the immunogenicity risk assessment “may be more problematic for monoclonal antibody products than for other products because of their complexity” and that the “risks may be variable even for the same antibody when used differently.”

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**MES’ VAN DER PLAS ON THORPE’S CONTRIBUTIONS IN THE BIOThERAPEUTICS ARENA**

*To mark Thorpe’s retirement from NIBSC after 30 years of service, MES’ van der Plas offered the follow toast at the MAb workshop – touting his contribution to the advancement of biotherapeutic product understanding and regulation. NIBSC became part of the UK’s Medicines and Healthcare products Regulatory Agency (MHRA) in 2012, explaining Thorpe’s reference to becoming a “proper regulator” below.*

**Van der Plas:** In 2006, I was at the 20-year celebration of the BWP. At that celebration, some very old documents were found and presented. One of these documents was for the meeting minutes of the first BWP, then called the ad hoc working party on biotechnological products of the CPMP. It was really very interesting. One of the decisions, apparently the most important decision, was ‘we need a guideline.’ The subject of the guideline was monoclonal antibodies. The guideline needed a rapporteur, and the rapporteur was, of course, Robin Thorpe....

I think it is important that you are one of the people that has really shaped the field of biologicals, biotechnology, and the regulatory assessment of those. Your contributions are beyond any clear indication of how big they are. On behalf of the European regulatory community, I would like to give this to you and thank you for everything that you have done.

**Thorpe:** That is too kind Martijn, too kind. And thank you for pointing out that I was at the first meeting. It was actually called the ‘Ad Hoc Working Group on Biotech Pharmacy.’ Nobody understood any of the words, and so they changed it about five years later....

So thank you very much for your kind words, and I think you know that was a gross overestimation of what I have done. But...I was able to do lots of things which probably would have been more difficult if I had been a proper regulator. So maybe that needs to be taken into account. One of those things was that then I would have been able to take these chocolates, but now I can’t since I am an MHRA employee.

**Van der Plas:** We will now toast and thank you for giving us your last talk under your organization.
What Data Can Be Extrapolated?

The discussions that followed Thorpe’s presentation at the PDA workshop centered heavily around the immunogenicity concerns and assessment in the biosimilars context.

Roche Biologics Regulatory Policy Head Thomas Schreitmueller set the direction of the discussions by asking for comment on how the issue of extrapolating immunogenicity data between different indications plays out for biosimilars.

Thorpe reaffirmed his “polarized” view on the issue. In the same vein as his presentation, he stressed the danger in assuming “that immunogenicity – and other things as well, but particularly immunogenicity – will be the same in different patient groups…because there are lots of good examples where it isn’t. If you really want to know what is going on from an immunogenicity point of view, you have to look for it.”

“Of course,” he added, “there are some sensible approaches you can take to this. If you are treating strongly immunosuppressed patients, then it probably means you are not going to see any worse problems.”

MEB’s van der Plas referenced EMA’s non-clinical/clinical guideline, which supports safety extrapolations to other indications once the most sensitive has been studied. With the caveats that he is not a clinician and that it is “the kind of issue where the thinking is still evolving,” he suggested the same logic “would apply to immunogenicity. You should look for the most sensitive indication, and in line with what Robin suggests, immunocompromised patients are not likely to be the most sensitive population in this respect.”

Noting that the immunogenicity assessment will continue post-approval, AGES’ Waxenecker commented that the ability to make the extrapolation would depend on the strength of the data.

Biosimilar vs. Biobetter

GSK Biopharmaceuticals Global CMC Regulatory Affairs Head Juan Gimenez, who co-chaired the workshop with BASG/AGES Clinical Trials and Preclinical Statistical Evaluation Head Ilona Reischl, brought up the case of a “biobetter,” where a simple change in the primary structure could extend the half-life and lower the immunogenicity because of the added spacing in the dosing regimen.

Thorpe joined with Waxenecker in stressing that biobetters are new products and have to go through a different regulatory pathway. Biosimilars have to have a comparable benefit-to-risk profile, Waxenecker pointed out.

Recognizing that there must be an underlying molecular reason for why there is lower immunogenicity, Gimenez asked for some generic examples of when this would be the case in the biosimilar context.

Before answering this “incredibly difficult question,” Thorpe pointed out that the finding could actually be an artifact, reflecting assay problems. “If is very important to have a way of assessing those,” he stressed.

If there is actually lower immunogenicity, the potential causes are myriad, he said, including differences in aggregation, the impurity profile, or the structure of the molecule in the patient. In any case, a reasonable explanation should be offered.

Waxenecker pointed out that biosimilars do allow for different formulations. He commented that “there is a good reason for that” in that the originator’s formulation may not have been maximized in terms of stability, chemical modifications or degradations, and that such formulation changes could have an immunogenicity impact.

Paul-Ehrlich-Institute Monoclonal and Polyclonal Antibodies Section Head Steffen Gross weighed in that the sponsor may get different responses from different regulators on these issues.

“If you make changes on purpose to reduce immunogenicity, I guess for many regulators you would get the opinion that this is not a biosimilar approach anymore.” However, Gross noted that “there is a discussion ongoing with the agencies and between the regulators” on where the lines should be drawn, and suggested that “one could give it a try and see what happens.”

Roche’s Shreitmueller pointed out the need to bear in mind that clinical endpoints used in these studies are not the normal endpoints and that a finding of lower immunogenicity may have other significance warranting further clinical evaluation.

“For example, if you look at oncology, you are not going for overall survivors, and we know that immunogenicity may impact safety as well.” As such, lower immunogenicity may have implications regarding “the true clinical endpoint you are looking for for certain products,” he said, suggesting that in that case it would be “useful to study the true clinical endpoint and not stop necessarily at some surrogate” like response rate.

Testing Immunogenicity on a Chip

Recognizing that Shreitmueller’s remarks “are well taken” and that “there is no uniform answer” to the concern
he raised, Van der Plas pointed out that “there is a clear movement” toward questioning the need for confirmatory clinical data and whether PK data or other surrogate data may be sufficient. “So there is a move to look for which surrogate endpoints are reliable and which are not” – a discussion he views as “taken very seriously.”

Later on in the discussions, Novartis Pharma’s Ursula Busse, a member of the workshop planning committee, pointed to the drive to replace animal testing with in vitro methods. Referencing the term “bodies on a chip,” involving “developing human organs on small microplates and using them to test drugs,” she raised the question if, sometime in the future, “this would be possible for an immune system? Could we copy the human immune system on a chip?”

Borrowing from Yogi Berra’s lexicon, MES’ van der Plas quipped that “prediction is very difficult, especially if it is regarding the future.” However, he noted that Europe is being pushed by its 3R initiative and animal welfare principles to “increasingly scrutinize the value of in vivo animal testing.”

While still required in many respects, “there is a clear tendency” to question if an in vivo test “really gives the answer” to the questions that need to be answered to approve a dossier. This is an “evolving picture,” he said, and one that his Dutch agency, in particular, is closely monitoring.

While the clinical data is still the final consideration, “we are looking for all kinds of in vitro methods that are at least helpful in this respect.”

Lilly’s Michael DeFellippis, who served with Busse on the workshop planning committee, summarized that “there are a lot of things that need to keep going in this area to make progress.” The workshop discussions, he said, offer “a flavor of where we are – the state of the art.”

At another point in the discussions, Genentech Bioanalytical Scientist Valerie Quarmby raised the issue of the powering of clinical studies to demonstrate biosimilarity pre- and post-licensing, “particularly with monoclonal therapeutics, which may have relatively low immunogenicity rates for reference products, even with the most sensitive indication.”

She asked for input, in particular, on “the thinking around how much immunogenicity data should be collected for biosimilars prior to licensure versus in the post-marketing setting.”

AGES’ Reitschl suggested that “simply because of the patient numbers pre-licensure…most of these efforts would be in a post-marketing setting.” Prior to licensure, “you would really only spot big differences and they would raise red flags for lots of reasons, not just for the immunogenicity.”

Reitschl added that biostatistics “is a topic that is gaining more and more momentum at EMA.” She noted that her AGES colleague Gunter Waxenecker and the EMA’s biostatistics working party “are getting more and more involved in that, and so I think you will be seeing documents coming out in the near future.”

What About Sub-visible Particles?

The discussion shifted at the session to what is known about the immunogenicity of particles smaller than 10 microns. A comment was made that FDA seems especially concerned with these small particulates. (See story on pp. 44-53 for more industry/regulation discussion of the small particle issues.)

“I think, in reality, the problem of how these particles relate to immunogenicity is hypothetical,” Thorpe remarked. “There is a lot of laboratory data showing that if you do things to molecules that makes them aggregate or form particles, or coacervates, or whatever, you might induce antibodies, you might not. It seems to be either way. So I don’t think you can say anything real about them.”

The problem, the NIBSC expert said, is that “people think they are there and…wouldn’t it be good if they weren’t there. Then you find that you can’t get rid of them, and so you are stuck with them. And so you have to justify why you think they are not a problem, or why you think they are a problem – whichever point of view you are trying to take. But in reality, nobody knows. Certainly I don’t.”

Waxenecker noted that the issue received attention at the first PDA-Europe monoclonals workshop six years ago on monoclonal monographs, “because in these monographs there was always this sentence that said, ‘should be free of particles.’” Since then, he noted, there have been many discussions between regulators and industry on what “free of particles” means. (ibid.)

“We don’t want to see foreign particles in the product of course, but you have proteinaceous particles that might be in there,” the Austrian official said. “These are, let’s say, flexible particles that dissolve and aggregate again.”

The European monographs have been changed to indicate ‘free of particles unless justified,’ Waxenecker explained, “and you can always justify that you have some proteinaceous particles in there. But what we would like to see is that you have characterized them – that it is really a protein particle, and you have the size, you have the minimum or maximum of what you could have.”

The current expectation, he summarized, is that the protein particles need to be justified, “but the intention as not to have foreign particles in the product.”
NIBSC’S ROBIN THORPE ON IMMUNOGENICITY ASSESSMENT OF MONOCLONAL ANTIBODIES

At a PDA Europe workshop on CMC and regulatory considerations for the immunogenicity assessment of monoclonal antibodies held in Basel, Switzerland in September, UK National Institute for Biological Standards and Control (NIBSC) Biotherapeutics Group Head Robin Thorpe provided his perspective on the MAb immunogenicity issues. Drawing from his extensive experience at NIBSC where he played a key role in advancing biotech regulatory standards and understanding, Thorpe’s presentation encompassed: ● the clinical consequences of immunogenicity ● current EMA guidance and expectations, and ● considerations for biosimilars. Thorpe retired at the end of October after 30 years at NIBSC.

Monoclonal antibodies, as you know, are a very large product class with probably thousands of monoclonal antibody products possible, and probably hundreds will actually exist. Many are approved for use, but a lot more are in development. They serve as therapeutics or as diagnostics where alternatives may not exist.

An important feature of monoclonal antibodies is that they are complex. They are relatively large, and they are hard to duplicate as they have quite a complex structure. This does impact immunogenicity assessment. They are all potentially immunogenic – this can cause impaired responses or rarely adverse reactions. They don’t really have endogenous counterparts, so immunogenicity is not a problem of the type that you see with things like EPO.

The structure of them: There are anomalies from completely non-human to what is called entirely human. From the immunogenicity view that isn’t terribly important because they all can be immunogenic, and some of the antibodies which are called entirely human or completely human actually are more immunogenic than some of the ones that aren’t. So really, although there is a difference, it is not that important when it comes to immunogenicity.

While there are aspects of immunogenicity that are specific among monoclonals, there are a lot which aren’t. Basically, monoclonals are just a biological, and so among the things that you would need to consider about immunogenicity of monoclonals are just those that you would consider for any biological. As you would know, biologic products can evoke antibodies, but these can have different characteristics. They can be non-neutralizing antibodies, called binding antibodies, against the active substance or product-related substances. They can be binding against contaminants. They can also be neutralizing antibodies. What you usually have is a mixture of the above.

This is problematic because you need different assays for assessing these different antibody types. That is a really important technical aspect, which I am not going to go over much because Gunther [Waxenecker, BASG/AGES] dealt with most of this anyway.

Clinical Consequences

So what are the clinical consequences of immunogenicity? These again are extremely variable. They can range from benign and non-significant unimportant consequences to really serious life-threatening consequences, depending on the therapeutic treatment.

The consequences on efficacy are usually a reduction of the clinical response. The consequences on safety can be variable, and certainly safety issues can occur when there is no loss of efficacy…

If you think about immunogenicity against monoclonal antibodies, it is very often the case that the development of antibodies, particularly with neutralizing antibodies in patients, can reduce the clinical responses to the MAb. The important word here is ‘can.’ There are a quite a lot of examples you can find in the literature where the reduced response is apparent. I have listed a couple of examples here: Remicade, Tysabir, Humira. Here it is quite clear that the antibodies you get can impede the clinical response. In other cases, like Rituximab, it is not so clear.

If you actually look at the literature, you will find conflicting reports, quite honestly, for just about any antibody. Sometimes it seems you do get an impairment, and sometimes you don’t. That is probably because of the way in which that is being evaluated rather than reality.

The unfortunate consequences of that is that it makes interpretation and prediction of clinical effects of antibody
development difficult and, in fact, nearly impossible. Generalizations relating to this are very dangerous. Having said that, generalizations are very often made. And the real problem with immunogenicity, the challenging issues, are that it is more or less impossible to predict the things you really want to predict such as: the incidence of immunogenicity; the characteristics of the immune response; and particularly, the clinical consequences of immunogenicity. These have to be assessed in appropriate studies, because you really can’t do much from a predictive point of view.

These are the so-called immunogenicity studies that Gunther mentioned earlier. The counter argument from a regulation position is testing for unwanted immunogenicity is integral to product development. It is part of it. It is the same as any aspect of it. Certainly it has to take place when the product is being developed, and also during post-marketing.

The reason that you do it when you have to do it, is first the obvious reason: for showing the clinical safety of a biotherapeutic. It could be a monoclonal or anything else. But also it is important for product comparability and when a biosimilar product is being developed. The issue of **biosimilar monoclonal antibodies** is particularly important at the moment. Currently there are a lot of these under development. I will cover some things specific to that at the end of my talk if there is enough time.

Alright, so how do you do the testing that Gunther already mentioned? I am going to go over it very quickly. You normally use this so-called ‘tiered’ approach. This is outlined in the guidelines. Basically you do a screening assay, which involves an immunoassay of some type. Then you normally confirm that. You have to run a screening assay, which detects all the positives because you are going to get some false positives. After that you normally do other things, such as doing assessment of neutralizing antibodies using neutralizing assays. This can be done using cell-based assays or non-cell-based assays….

**EMA Guideline on Immunogenicity**

Moving on to guidelines: The EU or the CHMP in real terms was the first regulatory body to produce a specific guideline on immunogenicity. It is quite a comprehensive guideline. It addresses just about everything you might think you need to address. But it is general, so it doesn’t deal with any specificities. It was produced and finally adopted in 2008, after quite a significant drafting period.

This is the regulatory guidance that we have from the EU. It is still in force, and it is planned to produce a re-draft…. It contains all sorts of valuable advice that I am not going to go over. It basically has within it bullet points of things that should be considered. This is just the [table of contents (TOC)]. I am not going to go through it *(see box at right)*.

What it does stress is the importance of having a **strategy for antibody detection** and a strategy in place as early as possible. If you don’t have it in place, you will get called out and you will find that you haven’t done something and that it is too late to do it. So it is very important to have a strategy. What all the actual strategy is is not terribly important, as long as it does have the necessary elements within it.
This is a strategy diagram (see box at right). You don’t actually have to use this one, but you have to have something like this. It should have the aspects, which are important, such as the way to discriminate between positive and negative samples and how you go on to produce this kind of overall assessment to immunogenicity as you see it. Then you see how you compare that with non-antibody assays, clinical assays, to see if the antibodies are actually doing anything important clinically. So you need a strategy. It needs to be something like this, but you need to produce this for each case if you like.

It is more problematic in some aspects for monoclonals than for other biologicals, which I will address in a minute.

As Gunther mentioned, there is a problem of pre-existing antibodies. These may be real or an artifact. The example that is almost always quoted is the problem with Erbitux, a monoclonal with an anti-EGF receptor. This is a real problem because the existing response was an IgE response, so you get this anaphalaxis problem. Having said that, this is a very unusual case that is quoted quite often. What you usually see in pre-existing monoclonal antibodies is that they are not IgE but they are IgG. They don’t necessarily cause a huge problem in the use of the product, but they do cause problems when you actually do immunogenicity studies because they cause all the artifactual positives. This is a real problem.

So that was basically the general immunogenicity guideline. It has been around now for about five years, and it has generally been well received. Nobody has said it is complete rubbish. Most people say it is good and others say it is okay. It certainly has been used by lots of people: manufacturers, regulators, and probably others. One criticism that has often been said is that it is too general because it doesn’t deal with specific products. When you read it, you can see that it is a bit of a problem.

So what would you do about that? Well you could write immunogenicity guidelines or sub-guidelines for just about every product. That is obviously not possible because the range of products is far too broad and certainly not necessary either. You would end up with a huge number of guidelines that would often contain a lot that is duplicative. This approach was not adopted, at least in Europe.

**EMA Monoclonal Immunogenicity Addendum**

It is certainly true that some products might merit specific guidelines. I think one glaring example of this is monoclonals for the reasons we said earlier. This is a huge product class with lots of products approved or in the regulatory approval process.

The outcome of this was that we have produced a specific guideline on immunogenicity of monoclonal antibodies. The front page of this is shown here. This was drafted starting around 2010, and went through a standard procedure for these kinds of guidelines by the biosimilars working party of the CHMP. It came into effect in December of last year, so it has been around for about nine months now.

Basically, this guideline is much shorter than the general guideline and is really obviously focused on monoclonal antibodies.
The original idea was to write it as an annex to the general guideline, because lots of the stuff in the general guideline is still applicable. So it would look like it should be an annex. We did originally draft it like that and we put annex on the front page. We were immediately disciplined by the lead people at EMA, who said the word annex is not appropriate here. Well I have been speaking English for 65 years and to me this seems like an annex, but not in the EMA. We have to take note of the lawyers, because otherwise you will go to prison.

So we did have ‘annex,’ but we deleted it. Christian Schneider, Gunther, and I – we all sort of discussed this, and thought ‘well, okay, there is nothing we can do.’ But when we set it up for consultation, lots of people said this should be an annex. We said, ‘well it can’t be an annex because annex doesn’t mean annex really, it means something else. So we don’t know what it is.’ This was unresolved until finally Christian Schneider, chairman of the bio working party, saw that somebody else had produced a guideline and they used the word addendum. And that’s allowed. So we just wrote addendum on the front and the lawyers said, ‘this is clearly an addendum.’ So if anybody can tell me the difference between an addendum and an annex, I would be really glad.

An important thing to remember is that this is to be read with the general guideline, so this is really a kind of an addendum.

In this guideline there is a lot of stuff that I think is important, but I am not going to have time to over this it at all. I think one thing that it is stressing is, it does say quite clearly, that monoclonal antibodies are a very diverse class. They are a huge class of products and they have a great deal of similarity between each other, but they do have differences. But monoclonal antibodies should not be viewed as a particular risk class because they can be different. The really important thing to stress is that very often it is said that monoclonal antibodies are a low immunogenicity risk. Well, they can be. They can be a low immunogenicity risk or they can also be a high immunogenicity risk or middle immunogenicity risk, and it depends on the monoclonal antibody and all sorts of other things.

So what is the new guideline actually aimed at? Well, they say it is aimed at development and systematic evaluation against an unwanted immune response against a therapeutic or in vivo monoclonal. It applies to all monoclonals and their derivatives, etc. It is aimed at products in the final stage of development, although it probably has relevance to products in earlier stages as well. It considers the major quality and clinical aspects that are important from the point of view of monoclonals. It really specifies certain things that have been considered important from an immunogenicity standpoint specifically for monoclonals.

**Immunoassays and Residual Antibody**

Just going through these briefly: it starts off considering assays. Gunther mentioned quite a bit about this so I am not going to belabor it, but in principle any immunoassay format can be used to measure antibodies against monoclonals. But in practice, it is more complicated than that. It is actually quite a challenge. It is more difficult to measure antibodies against antibodies than it is to measure antibodies against other things. This has got lots of technical issues and some aspects of this are mentioned in the guideline.

It also says that you really can have problems, which are often called matrix effects, with the assays you use when you are measuring antibodies against antibodies. This really has to be taken into account. It is much more difficult to set these things up and to have them performing in a valiant way than for lots of other products.

We say it is easy to measure antibodies against GCSF. But it is difficult to measure antibodies against monoclonal antibodies. And the real issue is that measuring monoclonal antibodies against GCSF isn’t really important because GCSF has never produced any antibodies, whereas monoclonal antibodies do, so it is really important to consider this.

A real problem is this residual monoclonal presence in the samples that you have to analyze. Monoclonals have quite a long half-life, so it is difficult to take samples that don’t contain the antibody. They are also used in relatively high amounts and even fragments of the antibodies can persist for days. This can really cause significant problems, and does cause problems. And really you have to try and do something about it.

There are all sorts of ways you can approach this, none of which I am going to go into here – except to show one thing
that people often don’t realize: actually selecting the type of assay can be important for this.

This just compares a classic two-sided ELISA for measuring antibodies against the monoclonal with an ECL [electrochemiluminescence]-based type assay (see box below).

### Detection of antibodies in the presence of therapeutic: ELISA vs ECL

<table>
<thead>
<tr>
<th>Reciprocal dilution of antibody</th>
<th>ELISA</th>
<th>ECL*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>OD 450 nm</td>
<td>Signal</td>
</tr>
<tr>
<td>50</td>
<td>2.5</td>
<td>10000</td>
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<tr>
<td>250</td>
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</tbody>
</table>

- Better sensitivity in absence of drug
- Higher dynamic range
- More tolerant of circulating drug

What you can see is that they both work, but the ECL assay is much more resistant to the effects of the residual antibody than the classic ELISA. This is because of the technical aspect of the ECL assay – the way it is actually performed. So by selecting the assay you can actually, to some extent, get round this problem. There are all sorts of other ways you can do this, but none, I should say, are perfect. But it is a real problem – particularly with monoclonal antibodies.

I think it is usually important to have confirmatory assays. You don’t have to adopt this tiered approach. Lots of people have done a lot of work to find other ways of doing it. But quite honestly, at least in my experience over the past fifteen years of doing these things, it is usually best to adopt the tiered approach.

The problem of controls is well known and still not resolved, and this is addressed in the guideline.

It is usually expected that you would measure neutralizing capacity that the antibodies induce. These very often are the important ones. That is particularly the case with monoclonal antibodies. With monoclonals it is a bit different to a lot of other biologicals in the nature of the way in which they work in binding to an antigen. It really means that if induced antibodies block the binding, then they are going to be the ones that are most associated with reduced clinical efficacy.

The monoclonal doesn’t have any inherent biological activities. It is not like depo or GCF or anything. It basically just binds. So very often in terms of neutralizing measuring capacity, competitive binding assays might be good, whereas they might not be good for some other products. In fact, with a lot of monoclonals, I think they are the assays of choice.
But this topic is controversial and a lot of people disagree with that, in fact. They like the use of cell-based assays, for example. In my point of view that is not the way, but it is case-by-case. It certainly distinguishes monoclonals from other types of biologicals where you really do need to do some kind of biological assay.

**Clinical Aspects - Risk Management**

Okay, that is the stuff on assays, and the rest of the guideline really deals with clinical aspects. This is addressed by risk management, if you like. It starts off by having a sizeable section on risk identification. It says things like, 'given that the immunogenicity of monoclonals is complex and often poorly understood, really assessing risk is important.' It goes on to deal with risk assessment and addresses this in some detail, and finally risk monitoring and mitigation. There is a lot of detailed information on this. It is quite clear, I think.

Following this, I think it is important to realize that monoclonals, though they are often considered as one group, are in fact pretty heterogeneous. There are all sorts of factors, which can make trying to make generalizations difficult and dangerous.

I have a few slides here that basically show some examples of when you can have problems. If you actually look at the frequency of antibody development in different patient groups, you can find that that frequency may differ significantly in different patient groups suffering with apparently different clinical problems. If you look in the literature you can find lots of reports—for example, Rituximab, when it was used in SLE patients, had a high immunogenicity at 65%. But when it was used in non-Hodgkin lymphoma patients it seemed to be hardly immunogenic at all. This reflects the patient group. To try and make a generalization about a particular monoclonal or monoclonals, in general, is just not possible, and you have to consider all sorts of other things.

Another example is where the frequency of antibody development may differ significantly in different patient groups suffering the same clinical problem, but may differ in some other way. The really clear example of this is with Infliximab (anti-TNF), which shows a higher instance of immunogenicity in children than in adults. This probably reflects the underlying clinical condition of the children — that children differ from adults. Again, you can’t make any generalizations.

Another example where antibody development differs in different patient groups suffering with the same clinical problem but differ in some other way is this one with Cimzia, an anti-TNF alpha-pegylated antibody, which induces significant immunogenicity in non-immunosuppressed patients at 12% but really much lower in immunosuppressed patients. You might think it is obvious, but very often when you see these reports it doesn’t say what the status of the patients are. That is very important. Again, you can’t make generalizations about antibodies without considering important groups.

**Biosimilars**

To finish off, I thought it was very important to consider something about immunogenicity of biosimilar monoclonals, because there is a huge amount of effort being put into these.

Recently one antibody, in fact, has been approved in Europe. I am sure there are going to be more — there are lots in the pipeline. This was anticipated by the biosimilars working party. They drafted a biosimilars guideline on this, which came into effect in December last year — the same time as the monoclonal immunogenicity guideline. This guideline deals with most of the aspects from the point of view of biosimilar monoclonals, but it also deals with and includes quite a bit about immunogenicity. It didn’t in the earlier draft, but it does now — particularly in the clinical aspects of immunogenicity.

It stresses the importance of carrying out comparability studies, as we have already mentioned. This is actually crucial in Europe if you want to consider the biosimilar route. It also mentions, as does the monoclonal immunogenicity guideline, that when you are trying to evaluate immunogenicity of a biosimilar, you are actually in the field of comparative immunogenicity, which is much more problematic than straightforward immunogenicity of a single product.

What you have to do is compare the immunogenicity of effectively different products because you don’t know whether
they are similar. You hope they are, but you don’t know that. Studies need to be designed to demonstrate whether the immunogenicity is the same or significantly different, because the important word here is ‘significantly.’ This certainly affects the design of the studies and their interpretation. You need a homogeneous and clinically relevant patient population, and you need to do head-to-head studies, and the same assays and sampling strategies should be used. These statements come directly from the guidelines.

Consequences of immunogenicity also have to be compared, and you probably have to continue this post-approval simply to build up patient numbers, so it is hard. Comparative immunogenicity is really difficult. It is probably the most difficult thing about the assay side of developing biosimilars.

Gunther already mentioned this **one-assay, two-assay problem**. It is actually a problem. How would you actually do it? I think it is worth stressing this. It is really important.

This is not in the guidelines, but it is based on the original strategy in the general guideline…. [To] carry out a two-assay strategy, basically what you would do is develop an assay, but you assay the samples using the reference product, the innovator product, and also the new product in the hope that it is going to be a biosimilar. The reason why you have to do this is because you don’t know that these two are the same. You hope they are, but you don’t know yet, so you can’t assume they are. So if you really want to have an accurate assessment of what you have from an immunogenicity point of view from these two products, you would have to do two different assays.

It is made more complicated because usually these studies are blinded, so you don’t know which samples you should be using for each of these. So effectively, if you really want to be comprehensive, you have to use all the samples for both assays. And this is quite a lot of additional work than if you just use one assay. But this is the really comprehensive thing. No one can really argue against this, I don’t think, unless you are going to try arguments about the performances of these two different assays, which you really have to deal with on a really technical level. But this is the two-assay strategy, which is pretty much foolproof.

The **one-assay strategy**…is basically pretty simple. What you do is you only use one product as antigen. I think this is fine from the regulatory point of view if you use the new product for certain biosimilars, when you hope it will be a biosimilar. That will mean you won’t detect all samples positive against that, and maybe not all samples with the innovator product depending on how similar they really are and how good this assay is at detecting antibodies against the innovator.

Of course the outcome of this is that you may actually have an underestimate of the immunogenicity of the reference product – which is not good when you come to compile your dossier because you will have to state that you have an apparent lower immunogenicity of your reference product, which may not be good. This is sort of a risk assessment really. You really have to decide, are you going to take this risk on board? And if you are, well that is up to you as a manufacturer, but it does have that risk. It does allow a much lower number of samples to be assessed.

The other aspect of the biosimilar antibody, which is important from the immunogenicity point of view, are the parts that deal with clinical issues, clinical safety. So it follows if you are developing a monoclonal antibody you really need to read the general immunogenicity guideline, and the specific monoclonal guideline. But then there are more things than that from a clinical point of view, and these are addressed in the biosimilar monoclonal antibody guideline…. It does spell this out quite well and clearly, which I think is really needed, because on looking through some of these applications for biosimilar monoclonals, there seems to be a lot to be desired from the immunogenicity point of view. It really does need to be looked at carefully.

Another thing we need to remember from a biosimilar point of view – and it has been ignored by some applications that I have seen – is that the immunogenicity of the marketed product, which is the innovator product, doesn’t influence the need for comparative immunogenicity studies. You can’t say, for example, ‘I am making a product that is like a G-CSF, and we all know that G-CSF isn’t immunogenic, so I won’t bother to do any immunogenicity studies because we know it isn’t immunogenic.’ Of course that is completely a flawed argument. What we do know is that antigens are seen to induce antibodies, but we don’t know about a new G-CSF. So these have to be treated as new products.

And really you just have to do the studies and you have to assess the outcome of the studies. Basically there are three
outcomes to these studies:

- If you are lucky, you show that the innovator monoclonal, and the biosimilar are the same, and if you have that, that is perfect.

- You might find the immunogenicity of the biosimilar is significantly higher than the innovator, and that has clinical consequences. In that case your product is dead because you have made something that is clearly inferior.

- The other outcome is that you have a lower immunogenicity of the biosimilar compared to the innovator, and this is really good from the clinical point of view. You have made something, that is, if anything, better. But of course, the problem from the quality point of view is that there must be some underlying scientific reason for that. And if it is real, then it might be that these products are dissimilar, which is not so good if you are trying to promote this idea of biosimilar.

So you would really have to explain that. Very often it would have to do with things like assays, which is fine, but you really do have to address that. You can’t just say, ‘our stuff is much lower because we have made a wonderful product.’

Okay so to finish off, I think it is true to say that immunogenicity issues occur more along the life-cycle of any product, including monoclonal antibodies, particularly when you are developing new products or a change is introduced or when you are proposing a biosimilar. Assessment requires an optimal antibody testing strategy, and validated methodologies, reference standards and all of these things.

I think it is also worth pointing out that risk assessment may be more problematic for monoclonal antibody products than for other products because of their complexity. Risks may be variable even for the same antibody when used differently.

That’s all I have got to say, I would like to acknowledge my [NIBSC] colleagues and also my colleagues in the biosimilars working party.
These companies and many others have committed to our global mission to protect patient safety by enhancing the quality of the supply chain and authenticity of materials within the supply chain.

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Building a system capable of finding quality problems through a firm’s pharmacovigilance program must begin early in development, one of the leading experts in the field, Lilly Global Patient Safety Senior Director John Ayres, is advising industry.

Ayres, an MD and an attorney, discussed the current state of the art in establishing the “GMP links to pharmacovigilence” at a meeting of the PDA interest group (IG) focused on the topic, held in conjunction with the PDA/FDA conference in Washington, D.C. in September. He is serving as the pharmacovigilance (PhV) IG lead.

“Your strategy very early on should be to establish the pharmacovigilence systems in such a way that you can pick up events of interest,” which are actually due to the product itself rather than “background” noise or other extrinsic factors, and understand the potential connections they may have to quality problems at either the manufacturing or supply chain level, Ayres commented.

He stressed the importance of development, CMC, and manufacturing working together through the product lifecycle to integrate safety and quality information with complaint and stability data to be better able to detect and even predict problems.

“We need to think of ways that we can, on a risk basis, look at our product attributes, and on the basis of the literature and our understanding of the classic molecules and so forth, be more predictive about how these can behave, and establish our pharmacovigilance systems to assist in that process,” Ayres maintained.

Lilly Expert Puts Key Issues on the Table

At the beginning of the IG meeting, Ayres introduced his co-leader for the interest group in Europe, Johnson & Johnson’s Agnieszka Majcher-Dann. Majcher-Dann is a qualified person for pharmacovigilance (QPPV) based in London and the Ukraine. Like Ayres, she is a physician, and is also a microbiologist. In addition to being a QPPV, she leads medical safety assessments at J&J as they relate to GMP issues.

Ayres went on to discuss:

● making assessments of product quality attributes on the basis of risk to the patient

● a continuous review process throughout the product lifecycle that involves pharmacovigilance and toxicology

● how safety signal detection and interpretation need to change to take GMP aspects into account

● what kinds of product monitoring should be done when outsourcing manufacturing

● the need in industry for physicians to have a better understanding of the technical aspects of the manufacturing in assessing clinically relevant issues, and

● future topics for the IG.

In the session, the Lilly expert outlined the key issues in the quality/pharmacovigilence interface that warrant more attention from the pharmaceutical community including: ● extraneous particulate matter assessments ● the methods for and utility of PhV and adverse event data mining ● manufacturing investigations for AEs ● risk assessment and monitoring for counterfeits ● clinical assessments and the design space, and ● PhV legislation impacting manufacturing and quality (Ayres’ complete remarks are included on pp. 47-53).

Involve PhV and Tox Early and Often

Ayres highlighted the benefits to be reaped from the mutual involvement of PhV and toxicology experts at each product milestone (see box below).

A Continuous Review Process at Relevant Decision Points

Ayres stressed that PhV and tox experts should be included in the assessment process at each of the following key decision points, and that both internal data mining and individual case reports should be reviewed.

Candidate Selection First Toxology First Human Dose Phase 1 Phase 2 Phase 3 Prior to Submission Post-Approval Safety Studies Periodic Safety Reviews

He advocated taking the opportunity at each milestone or “relevant decision point” to “more critically assess the product, complaint information, stability data, accumulated
At each point, any signals picked up by the system should be brought up and examined to determine if they have any relevance to the decisions being made, Ayres maintained.

“Maybe we have gained knowledge over the time that this product has been on the market or through studies so that we can modify it to either increase its therapeutic window and make it more efficacious or decrease its risk to patients,” Ayres commented.

The idea going forward, he explained, is to have data sets with higher degrees of certainty, allowing better articulation of the benefit/risk during the discussion at the end.

“This is opposed to what I think has been historically done, where folks kind of sit around like the Maytag repairman waiting for clinical trial data to be completed. The statisticians work on it. And then there is a vertical assessment – ‘what are the good things around this drug? What are the negatives? And here is the benefit/risk.’”

**Joint IG Meetings Proposed**

Ayres envisions the IG as a vehicle for bringing a cross-functional industry group together to evaluate the available data and what gaps need to be filled.

He suggested the possibility of joint meetings with other PDA IGs – e.g., visual inspection, quality risk management and quality systems – and perhaps setting up a session at a PDA meeting outside of the interest group to focus on the GMP/PhV link topic. Ayres also suggested more frequent IG communication in the form of online interim meetings or web collaboration sites.

**During the Q&A after Ayres’ presentation, Baxter’s Krista Hartman expressed her support for joint interest group meetings.**

Hartman noted that at Baxter, pharmacovigilence reports into the quality organization. This structure has created “a really unique opportunity to work with the clinicians when we do things like design and process FMEAs and look at the HACCP situations and link it, most importantly, to the process FMEAs – so that when we make design changes or we make process changes there is a consultation back to pharmacovigilence.”

She commented that she had not, prior to going to Baxter, “appreciated” the linkages. “It is a highly collaborative environment in which we work with the clinicians and the MDs to really do correct assessments and look for the right safety signals.”

**How Important are Particles?**

After his presentation, Ayres opened the session up for discussion of the key issues that he had highlighted as warranting further consideration.

**Drawing attention, in particular, were the issues around particles and their connection to the quality of the product (see also story on p. 31).**

During the discussion, Ayres’ opined that the problems associated with macroscopic particulates are “overrated.” A large particle – for example, “a chunk of glass 700 microns across” – he said, is not going to be drawn into a syringe, and “anybody in their right mind is not going to use it.”

Sub-visible particulate levels, on the other hand, are “counter-intuitive,” Ayres said. According to USP <788>, a parenteral product can contain “600 particulates per container that are 25 microns or greater – as long as you cannot see them.” He “would much rather get something that had a rock in it and say, ‘well, I am not using that’ as opposed to not knowing what I cannot see.”

Ayres noted that USP has begun a re-evaluation of Chapter <788> on “particulate matter in injections” and will be writing a new chapter specifically for therapeutic proteins <787> and macroscopic <790> particles.

Also in the works is informational chapter, <1790>, which includes a discussion of the safety considerations. Ayres is on the expert panel that is writing the new chapters.

He explained that the panel will be addressing the definition of “essentially free,” and that Chapter <1>, where the term appears, will also need to be revised. If the goal is “particulate free,” that term will have to be more clearly defined. “Are you going to eliminate sub-visible particles?” Ayres asked, commenting, “probably not.”

The panel would like to “put some rational basis” around the particulate expectations in terms of safety and process capability. Ayres envisions a two-step process that combines USP expectations and patient population requirements.

“What goes in to what we manufacturer that is going to be used for infusion through an umbilical catheter in a 1 kilo baby is very different than what you can give to me,” Ayres stressed. “And I think that the standards on [the former] should be as tight as a drum. If you are going to be in the business of doing that, it has to be that way.”

Ayres pointed to comments the USP panel has made regarding the importance of particles, noting that they are “very, very small.”
received that indicate the need for better definitions and understanding of expectations for particles as well as an understanding of fundamental quality principles.

Some companies, he said, interpret “essentially free of particulate matter” to apply to individual vials rather than to a production batch. They believe that if each vial – rather than each batch – has a few particles, that is not a problem.

Other firms, he said, do not have “rejects” in manufacturing, but “ejects” – units that do not meet specification and are ejected from the batch and not distributed. “So if they have particulate matter, the automatic machine is ejecting these. They don’t care if their yield is only 40%. That does not constitute a quality issue to them, because they are able to eject it.”

Both situations are counter to current quality principles, Ayres stressed. He also commented on recalls for parenteral drug products that contain particulate matter and the mixed messages that are sometimes sent.

If a distributed product contains particulate matter, it should simply be deemed adulterated and recalled, Ayres said. In situations where a recall may result in a drug shortage, he noted, too often a “dear health care provider notice” is sent, instructing the physician to inspect it for particulate matter prior to use.

“You are sending two different messages,” he pointed out. “It is either not safe to infuse or it is adulterated and it is not going to be on the market. We need to start making those distinctions better.”

**All Particles are Not Created Equal**

Continuing on the topic of particulates during the Q&A, CDER Office of Drug Security, Integrity and Recalls (ODSIR) Associate Director for Risk Science, Intelligence and Prioritization Steve Wolfgang honed in on the causes of particulates and their relative sizes, and how they may be treated differently as a result.

Better understanding of what the particles are and where they come from – including sub-visible particles – could be useful, he maintained, to understanding and avoiding them.

“What are those particles? How did they get there in the first place?” Wolfgang asked. “You have extrinsic and intrinsic particles. You have particles that are there for common cause variation and particles that are there for special cause. It seems to me that industry has not really gotten to the point where they understand this problem.”

Ayres agreed with the ODSIR official, and emphasized the importance of a third category of particles – those inherent in biologics that may interact with the product molecule.

“As you are putting together a biologic product and its delivery system, it is important to think about the potential interactions of the product,” Ayres stressed. “The question that we are going to have to grapple with, and are starting to now, has to do with the sub-ten micron particles and metallic particles, in particular. If you pick up a fragment of a monoclonal or a protein, and it lays back on the particle and expresses an array of epitopes such that it gets engulfed by a macrophage, all of sudden it might enhance immunogenicity.”

The potential for this kind of interaction points to the need for early discussions in the selection of materials for the delivery system, he maintained, noting that the most common particulates in parenteral products come from drug interaction with the container closure system.

Ayres pointed to insulin, which Lilly manufactures, as a case in point.

“I am very interested in the fragmentation characteristics of the seals and the stoppers,” he said, because insulin is taken multiple times each day over many years and any particulates in the product can accumulate in the patient.

Ayres commented that there are patients who have been taking insulin 75 years. “Can you imagine what kind of particulate burden they may have subcutaneously?”

He explained that about seven or eight classes of materials comprise about 95% of particulate problems. For firms using those materials, he suggested investigating the possible impacts of particulates in their products – for example, whether they may impact effector function or combine with the drug substance.

Wolfgang commented that, “if you are talking about a drug that has been made for 35 years with no metal shavings in it, and then one day you have metal shavings in there, and something happens that they are sub-visible because they are in a suspension that is milky white so you cannot really see them unless you let it sit for a few days – to me that is a serious issue, even short of patient safety. Why would you want to take the risk and continue to make the product when you know you have an abrasion problem?”

“Absolutely,” Ayres replied. “I don’t think there is any argument around that. We have an opportunity to sort of narrow this down, and with clinician input to do some more thinking around the impact of particulate matter.”

Ayres hopes to increase the “non-regulator physician” IG membership and “build a core group of people that are probably already working with these issues.”
I am John Ayres, [Global Patient Safety Product Safety Assessment Senior Director] and internal medicine physician from Eli Lilly. I have been at Lilly and in the industry for ten years. I am an attorney as well. For the past ten years I have worked at Lilly in safety, primarily supporting quality and manufacturing, and subsequent to that, development – where we are thinking about ways to integrate safety into the lifecycle of the drug product and to establish ways to better understand our clinical trial information on the basis of drug product attributes. We started this forum last year, and we are going to try to continue to build and pursue it.

What we are trying to do is create a forum through PDA where we can get to some of the points that are listed here (see box at right).

I won’t spend a lot of time on them, but basically it is what I mentioned at the outset: How can we work together with development, CMC, and manufacturing through the lifecycle of the product, and think of better ways to understand the behaviors of our products in patients?

When we are looking at spontaneous adverse event reports, our best guess is that we get only about 10-15% of all reports. We are trying to manage our understanding of how these products work in patients on the basis of very limited information. Clinical trials obviously cannot be powered enough to pick up every safety signal that could ever emerge.

So we need to think of ways that we can, on a risk basis, look at our product attributes, and on the basis of the literature and our understanding of the classic molecules and so forth, be more predictive about how these can behave, and establish our pharmacovigilance systems to assist in that process.

We need to make better decisions about our products early. If a product is not one that can be commercially successful or provide the benefits to patients that we want, that is a good time to stop and not to continue to invest hundreds of millions of dollars.

On the other hand, we might find attributes that are responsible that can be modified in such a way that now we have a product that can be life-improving or life-saving with a reduction of its safety concerns in such a way that we do not throw a good molecule on the scrap heap because we have attributed its problems to something that could be correctable. It is also good to understand what the limitations of our pharmacovigilance systems are.

Risk-Based Assessments from the Patient’s Perspective

In the opening session, [CDER Director] Janet Woodcock provided her view of the path forward. She is suggesting that it is time for us to start making our assessments of product quality attributes in the product on a risk-basis from the patient’s perspective. She suggested assessing dosage forms with predictive failure modes. That would make some
sense. I know there have been a number of groups that have come together and looked at how you would vary the attributes of either small molecules or biologics in such a way that might make some difference.

A couple of years ago I was at a presentation by [Office of Biotechnology Products Director] Steve Kozlowski, who suggested that it would be nice, if instead of trying to put within your clinical trials a single form of a drug substance, that you had two or three variants to better understand how those differences might play out.

From an industry perspective, the pushback was, ‘wow, that would be very different and that would be expensive.’ That was what they were concerned about. But the kinds of things that we heard on Monday from [FutureMed Executive Director Daniel Kraft] suggest that it may not be that way in the future. If we can lay the tracks to be intersecting with the possibilities of new technology, we are going to be ahead of the game.

I do think it is incumbent that we eliminate unacceptable errors – we do not want to do the equivalent of cutting off the wrong foot, like some of my colleagues in medicine do apparently routinely. These should be CQAs [critical quality attributes]. The CPAs [critical process attributes] that I work with are not always clinically relevant. We need to define what is not important in the patient. I think that is an important element as well.

Continuous Review Process

So where does this take us?

Traditionally, pharmacovigilance and toxicology are engaged at various points. But what we are suggesting is that at each of these milestones, at each of these relevant decision points that we have in the development and selection of a drug candidate through our trials and through the life-cycle, that we take the opportunity to more critically assess the product complaint information, stability data, accumulated tox data, and any clinically relevant patient data, and ask ourselves questions about if it is going the direction we want to.

Are we seeing signals? Maybe we have gained knowledge over the time that this product has been on the market or through studies so that we can modify it to either increase its therapeutic window and make it more efficacious or decrease its risk to patients.

One example of this that we have developed and worked on is within development, where we are bringing very early questions even if we do not know them. We have used this particular model (see box below) to look at the attributes' impact and assess that, in addition to the degree of certainty that we might have relative to the information, such that the impact score could be high if it is a new molecular entity where there is not any literature and you do not have your tox data back or whatever.

### Attribute Assessment and Impact Model

<table>
<thead>
<tr>
<th>Impact Score</th>
<th>Biological Activity</th>
<th>PK</th>
<th>PD/Efficacy</th>
<th>Immunogenicity</th>
<th>Safety &amp; Tolerability</th>
<th>Toxicity</th>
</tr>
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<tbody>
<tr>
<td>High (9)</td>
<td>&gt; 50 – 100% Change or No data</td>
<td>change in PK is linked to quality attribute OR Significant change in PK with no connection with quality attribute OR No change in PK detected but metabolism results in significant loss of PD linked to quality attribute OR...</td>
<td>Significant impact on PD that appears to be attributed to specific quality attribute OR Significant change in PD with no clear link to specific quality attribute OR ... ETC</td>
<td>ADA detected that appears to be linked to specific quality attribute and has a significant impact on PK/PD/Safety OR ADA detected that has no specific link to the quality attribute but has a significant impact on PK/PD/Safety OR No data available on ADA in relation to specific quality attribute OR...</td>
<td>No Data Available OR No margin of safety OR Cytokine Release Syndrome Grades 3-5 (see Appendix 1) OR...</td>
<td>Data suggests that the attribute affects the conduct/interpretation of the toxicology study (i.e. presence of aggregates). OR The test article has a less than typical margin of safety to clinical doses OR...</td>
</tr>
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</table>

Incorporates attribute's impact to pharmacological properties and the knowledge basis used to determine the impact (i.e. uncertainty).
In this way, we can start characterizing our attributes as either having a high, medium, or low potential patient risk, and focus on the areas where we lack the data that we can build.

Again, the idea going forward is that the better your data set, the **higher degree of certainty**, and the better you can articulate the benefit/risk during the discussion at the end. This is opposed to what I think has been historically done, where folks kind of sit around like the Maytag repairman waiting for clinical trial data to be completed. The statisticians work on it. And then there is a vertical assessment – ‘what are the good things around this drug? What are the negatives? And here is the benefit/risk.’

And then, because a lot of our therapeutic areas are pretty crowded, people will flip it and say, ‘how does my molecule compare to yours? Is my safety profile better?’ And so forth. I think we can move all that forward and get it really early in development and start thinking about these things a little bit more carefully. Because as an industry, in the small molecule world, there were opportunities twenty years ago, twenty-five years ago when I started practice – a lot of these therapeutic areas were not very crowded. But if you are out trying to develop a second line therapy for rheumatoid arthritis, it is a fairly tight landscape.

And if you are going to invest, from a social standpoint, a lot of money in that, you really need to define very early the endpoints that you want to receive relative to the benefit/risk and see if it is really going to help the patients. That is where we can start getting patient advocates in as well to help guide us in the therapeutic decision-making.

**Safety Signal Detection**

For those of you that do not spend a lot of time in pharmacovigilance, I want to remind you that when we receive an adverse event report from a patient, the scientists and the physicians that are working on that, their brain kind of locks in on ‘this is a perfectly acceptable drug, it has been manufactured, it is pristine, there are no problems with it.

And so the event that is being reported to me is related to the drug substance, or the excipients, maybe the related substances, or there is some nuance associated with the patients, maybe an idiosyncratic reaction.’

I know one of the shocking things that occurred to me when I came into the industry ten years ago was that I had no idea about the complexity, about the scale, about all the things that can go wrong. I was naive, as I think most of my colleagues are.

I consulted with a distinguished university professor of pediatrics about a question that we had with an oral dosage form. And in our discussions we were talking about the bioburden of the API and the evaluation. And he said, ‘you mean these pills aren’t sterile? Wow.’ No, this is not sterile manufacturing.

And that is kind of what happens. The marketing folks have done such a good job, I guess, and historically our industry has been so well managed and regulated, that my perception was really the same. I just did not think about it. It comes in a sealed bottle with a little cotton plug. This is all good. So again, it is that understanding.

The docs and the scientists working in pharmacovigilance, I think – because I work with a bunch of them and I talk about what I am concerned about, which [includes the quality aspects] – have the tip of the iceberg when they get an adverse event report.

I am interested in manufacturing issues: **The label**, especially as you look at the truth copies being sent electronically to other markets overseas where they are going to be translated. How many times does a Greek ‘µ’ for micrograms gets converted into an ‘m’ because of some glitch in the transmission associated with a word document? It is just that kind of thing. So if you see events and you are saying, ‘wow, this is a terrible molecule,’ then go back and say, ‘look at the label.’

Marketing and promotional items, like **dosing calculators**: As a medical student I proudly received a slide rule to calculate dobutamine infusions. And I relied on that. Well, as we put these things out to caregivers now on parenteral medications, they must be fully qualified. You cannot let your affiliates download the source code in order to come up with some little marketing gizmo, because it does not take very much to knock these things off stride. Do not let them
use decimal points, because you can lose that and all of sudden someone is getting a 10x over or under dose on the basis of some glitch.

The thing we have heard most in this conference and others are the counterfeit, substitution, tampering, and similares – those sorts of things that can induce a false signal. So the GMP interface, the place where quality is involved in pharmacovigilance primarily is on this lower set (see box at right). And that is what we are interested in ferreting out in the safety signal discussions.

The next thing to be aware of is that you cannot discover everything with a trial…. I have taken this from an article that was published in 1977 in the New England Journal of Medicine. Think about the rate of the suspected drug-induced illness. Consider all of the issues that I showed in the previous slide that were below the waterline against the background rate and how you can detect these events. Your strategy very early on [should] be to establish your pharmacovigilance systems in such a way that you can pick up these events of interest on the basis of the background rate in the community versus what you might expect from the drug.

A couple of examples: Say you have an oral dosage form that could cause indigestion, but it is going to cause it one in a million patient years. 75% of people carry Rolaids around in their pocket, so you are just not going to discover that crazy thing. On the other hand, if you look at, let’s say a rash from first generation cephalosporins, that incidence is about 2.3-2.5%. That is much higher than the background rate, and that is pretty easily discoverable, not only through formal research but certainly in clinical observation.

Then you have some real tough ones. I will take on a molecule that we have – teriparatide, or parathyroid hormone, where in pre-clinical work in rodents there was a development of some sarcomas and osteosarcomas. So the question is, is that an effect of the API – the drug substance – or did it just happen to a bunch of unlucky rats? And what about humans?

If you have a very low frequency event in humans – maybe one in 200,000 for adults over 65 – you have to develop a registry over years and years and years to be able to identify an emergence of a signal associated with that, because we have not seen an incidence that has been associated with patients receiving this on the drug product over a period of time. That is the kind of thing where you are going to have to establish a very long, 15 or 16 year study, where you are going to have to figure whether or not that is implicated.

Occasionally, I will get a phone call and somebody will say, ‘we have such and such of a finding with a product complaint. Can you query the database to see if there is a problem?’ Well, it is not quite that easy. You have to understand what you can pull from this limited dataset, especially from this pharmacovigilance data.

The types of product assessments that we do are prospective and retrospective. There is an opportunity to use this information and to bring the clinical side in for things such as change control or stability batches and so forth. I will give you an example of that.

Ultimately it comes down to this: We have deviations or excursions and product complaints, which are a source of information that results in a manufacturing investigation. And the questions that come in after that investigation [include] whether there is a potential impact on patient safety. That is where your clinicians can perform a safety assessment, a medical assessment, and consider from that the potential adverse events that might arise.

But you can also do this the other way. You can data mine in your pharmacovigilance database and look at the other
events. And if you see a potential signal emerge, you can ask the question the other way: ‘I have a cluster of events on a particular batch. Is there something different about this batch that maybe was missed or resulted from handling or transportation or an environmental excursion?’

Again, you [should] consider the biologics that are coming forward and the fact that you can have a lot of things happen on the basis of handling. We have situations – FDA has obviously been very engaged in this – where oncology clinics, for example, are importing drugs through Canada or other venues where there have either been exposures in mishandling or substitution of counterfeit or substandard drugs.

If you are looking at your adverse event database and you are not thinking about that as a possibility for your product, you are trying to evaluate a nonsensical signal and attribute it to your own product when in fact it could be due to something else. There are opportunities to set your pharmacovigilance systems up to do that. Obviously, you have to have quality oversight as you build this together.

It does really come down to the culture of quality. It not only has to be in the manufacturing environment, but you have to have quality systems in medical, in marketing, in pharmacovigilance, and in regulatory. You have to have this fully integrated to really support the work you are trying to do with your adverse events.

**Contract Manufacturing**

As a hypothetical example, when we do a site change for a product that is at the end of its lifecycle, we may want to have a third party contract operation manufacture it. I like to flag those batches that are going to be produced from that new manufacturer, whether it is drug product or drug substance.

And then you can perform a side-by-side analysis using different methodologies and ask yourself, ‘am I seeing any difference in my safety reports?’ recognizing they are spontaneous, so there are limitations. But on that basis ask, ‘are we seeing any differences? Is there something different emerging in this?’ Because if you do not ask the question and do not set your systems set up to look for it, you are never going to find it.

And you can do the same thing on stability batches – if these are in the market and you put them on stability for a particular reason. Change control is another way to do it. It allows us to use the information that we are getting, because the patients and physicians are telling us something about our products and we do not want to ignore that. Even a single event that is going to tell you that there is something different about this. You will only recognize that if you are looking for it and if your systems are set up to detect it.

Here is an example of a stability batch where what was filled would probably not be an issue. In this example it was not a serious issue. But there were differences in the reports that we were identifying for injection site reactions and so forth. It is, again, a way that if you are looking for it, you can set your systems up to identify it.

**Clinically Relevant Issues**

To go back to Dr. Woodcock’s statement, when do you do that? When there is a potentially clinically relevant issue that presents itself. And that is easy to say. But if your systems are not set up to incorporate that input, you are not going to get it. The other thing is that you do not want your docs sitting in every meeting. It is not a good use of their time. Plus you are going to have most of us that are not really going to understand much about what you are talking about.

There are two points here: One is that we need to start developing education programs within the industry for physicians to have a better understanding of the technical aspects of the manufacturability of our products – how those happen, what can go wrong, and so forth – so that they can participate in these discussions.

And those of you on the other side of the table also have to change your way of thinking. I would suggest to you that if you find a macroscopic particulate in a parenteral medication – say you get a complaint for a 300 micron something in there, a particle – then you send that off to the lab, send it to forensics, and you get somebody else’s perspective on this. They give you some technical information back. When you are looking at an excursion or deviation and the
product is on the market, I think the tendency is to ask, ‘what is the root cause? Let’s do the investigation. Let’s gather all this information.’

I will bet there are very few – I hope that I am not right – that are set up to pick up the phone and call pharmacovigilance and say, ‘we have this event, is there something that we should be thinking about relative to our investigation that is going to be more important or clinically relevant for you?’ Because my experience has been that sometimes the work that is done is overkill.

If I am looking at organic leachables – for example, from gasket materials – I am more concerned about the sum of those leachables than the individual components. As long as they are below 1.5 micrograms of exposure per day, I am good to go from a safety standpoint. So do not go spending a million dollars trying to do a bunch of experiments – calling your gasket supplier trying to get proprietary information that they do not want to give you about what they do and what they use. Call somebody in safety and tox and say, ‘what do you need to know? What do I need to give you to make an informed safety decision?’ And that is where I think you can start bringing people in.

Where can you do that? I think the bang for the buck is going to be in the design space. I really do. I think, if you can start getting input into your critical quality attribute discussion, that you are going to see a good return on your investment and a better understanding on both sides of the table on the performance of the product....

I get a lot of questions around this: ‘Is trending out of spec a problem?’ I ask, ‘how did you come up with this number?’ ‘Well this is from twenty-five years ago.’ You need to have those perspectives to bring the challenge to establish the specifications in a way that they have more clinically-relevant meaning. Or simply put them aside and say this is strictly a regulatory GMP question and deal with it that way. The reason for this is that I think it provides a holistic assessment.

I try to remind my colleagues that just because I say something is safe does not mean that it will not need to come back in on a recall. It does not mean that it is good to release to market. I am simply telling you that it is safe. There are a whole lot of other things that people have to do. It is really important as you are working with your clinician to not go running down the hallway shaking this and saying, ‘Dr. Jones says it is okay.’ I have a lot of friends that I respect that work with the regulatory agencies, and they really do not care about my opinion on whether or not a product should be released. They are happy that I am weighing in on the safety. But that is not my job. I am not a QP. I don’t release products on the market. And do not use my opinion to do it....

I will review deviations to look at the rationale that is used on why someone does not believe there is a safety issue or something. In one of them I was reading a discussion around cleaning and a residue of isopropyl alcohol. And they said, ‘Dr. Ayres reviewed the cleaning protocol and said that it was okay.’ I did not say that. What I did say was that isopropyl alcohol at 180 ppm in this API was not going to be translated into a patient safety issue. That is really different. I do not approve protocols. I would not have the first idea about how people climb into a tank or whatever they do. So you have to recognize what the limitations are that we have from safety and use those appropriately.

Future Topics

I was invited a couple of years ago, by [industry consultant and PDA Visual Inspections Interest Group leader John Shabushnig] and his group, who were interested in the topic of extraneous particulate matter assessments, to participate in their forum along with some regulatory colleagues. What we are really asking ourselves is, ‘what are the clinical implications of particulate matter in parenterals?’

My [personal] position is that macroscopic particulates are overrated. If you get something, a chunk of glass in there that is 700 microns across, it is not going to be drawn into the syringe, number one, and number two, anybody in their right mind is not going to use it. And to qualify that with ‘right mind,’ you know what I am saying.

On the other hand, look at what we accept for subvisibles – we are all fat, dumb and happy walking down the hallway because this is made under <788> where you can have 600 particulates that are 25 microns or greater as long as...
you cannot see them. So to me that is all counter-intuitive. I would much rather get something that had a rock in it and say, ‘well, I am not using that’ as opposed to not knowing what I cannot see. And just so you know, there is somebody that works in this business that thinks that that ought to be tightened up, because I have looked at it. Before I came to Lilly, I did consulting, and I understand that it is different product to product, but our process capabilities are really good. You have to be proud of what you can do relative to the amount of subvisible particulate matter that we have in our parenterals.

But do not sit back and say, ‘oh, don’t change that because I don’t want that stuff coming out at 580.’ I was in the emergency room in January, and they were going to have to give me some medication, and I asked, ‘who made that? Can I see the vial?’ I was all over it because this is very different for me now.

We can talk about product complaint and adverse event data mining and how we can pull those together, and manufacturing investigations for adverse events. That is all over the board as far as I am concerned.

Some companies do a lot of investigations. And then I have read some 483s and warning letters where some people say ‘we never had any other reason to look because it is all so good, what we do here.’ And we know that that is not true either.

Portfolio risk assessment for counterfeits: Which of your products are more likely to be counterfeited? Do you have a process in place to ask that question? What sort of anti-counterfeiting features are you going to put on your products? And how do you do that assessment? I think that safety clearly has a big role in that.

We talked about clinical assessments and the design space.

And then an opportunity to understand pharmacovigilance legislation – for example, what was passed in the EU in the past couple of years and its impact on manufacturing and quality and some of requirements that came through. Is there an opportunity for us to think about those things? Because that might provide us an opportunity for white papers through PDA and to collaborate as has been done more on the technical side around these interface issues, so someone doesn’t jump out in front and have expectations of capabilities that maybe don’t exist.

I think it would be good, in my opinion, to take one of these sessions at PDA/FDA and have it focus solely on these interface issues. Take an hour-and-a-half and get a couple of speakers and develop that a little bit more.

Should we have some sort of online interim meeting, web collaboration sites, or joint meetings with other interests groups? That was part of the discussion. The quality risk management interest group may be doing some things that can tie in very closely with what we would like to do.

That is really all that I wanted to get out on the table for a potential discussion. We will open it up for comments, suggestions, questions and we can go from there.
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