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FDA Deploys Risk Ranking Process to Streamline ANDA Review

FDA’s generics office has developed a risk assessment algorithm for the review of abbreviated new drug applications (ANDAs) to help address the challenges of balancing more extensive quality-by-design-based submissions with the foreshortened review timelines mandated under the Generic Drug User Fee Act (GDUFA).

At a Generic Pharmaceutical Association (GPhA) CMC Workshop in early June in Bethesda, Maryland, Office of Generic Drugs (OGD) Chemistry I Division Director Andre Raw described the risk-based review process that OGD has now instituted for ANDAs.

In his presentation, Raw covered: ● the drivers for the new risk-ranking approach ● how OGD’s question-based review (QbR) and quality-by-design (QbD) efforts helped inform it ● how it was developed ● how it works ● success to date, and ● future plans, which include the application of the concepts in the new drug arena. [Editor’s Note: Raw’s complete remarks are included below.]

Misassumptions on Workload Factor In

Raw explained that during the GDUFA negotiations, OGD assumed that applicants would withdraw applications once the user fee requirement went into place and that, based on historical data, the agency would continue to receive about 700 applications per year.

Both assumptions proved to be off target. Less than 10% of applications have ended up being withdrawn, and the rate of applications received has exceeded more than 1,000 per year.

The confluence of these factors – in combination with the shortened review timelines mandated under GDUFA and an increasing percentage of ANDAs containing “an explosive amount” of QbD-related information – created a significant resource challenge for OGD.

In a natural progression from the office’s 2005 institution of QbR and its publishing in 2011 of QbD examples, OGD turned to the risk management principles laid out in ICH Q8 and Q9 in an effort to solve the problem.

With resources divided relatively equally among the applications it was receiving, Raw noted that some lower-risk applications with extensive QbD information were taking an inordinate amount of review time. Conversely, more complex applications that were higher risk may not have been getting the proper attention in a timely manner.

The situation prompted Raw and other senior OGD officials to develop a method to prioritize application review based on an initial assessment of the potential risk of a product failing its critical quality attributes (CQAs) – taking into account the probability of failure and the severity of the harm it could cause.

An initial ranking of about 100 applications using a semi-quantitative, preliminary hazard analysis (PHA) approach helped reviewers focus on where the risk factors were in formulations that should receive the most time and attention.

Raw characterized the results as “a very big success” that the reviewers “really liked.” The process was further honed by switching to a failure modes, effects, and criticality analysis (FMECA) methodology that is less subjective and focuses on the risk to the patient – a tool the OGD official touted as “very powerful.” A pilot was conducted using about 350 immediate release (IR) product applications.

“We have data showing that, especially for the low and medium risk products, it really does increase the efficiency of our review,” Raw commented. “For the high-risk products, it really focuses the reviewer on the high-risk elements. So it was a tremendous success.”

As a result, risk management has now been formalized in ANDA reviews.

“I can tell you that every single IR product that is reviewed has an initial risk assessment using this algorithm,” Raw pointed out. “It tells us what the initial risk is, and that will help focus the reviewer on the areas of high-risk. Conversely, if there is a not very high risk, then they do not have to spend that much time on it.”

The expectation for reviewers – which include formulators and chemical engineers – is that they provide a discussion of how the risks they find were mitigated based upon the information in the application. Raw pointed out that if the risk mitigation information is not included in the application, then OGD will likely issue a deficiency letter to the applicant.

The OGD director explained that the new risk ranking approach does not impact what OGD expects to see in ANDAs.

Editor’s Note: Raw’s complete remarks are included below.
The office’s expectations were recently clarified in a draft guidance on the “content and format of ANDAs,” released in mid-June for a 60-day comment period (see story on p. X). The guidance details the information to be provided in each section of the common technical document (CTD) and identifies supporting guidance documents and recommendations issued by the agency to assist in preparing submissions.

The draft is intended to complement previously published guidance on the filing process, including the refuse-to-receive standards, which the agency advises “should be reviewed thoroughly to avoid common deficiencies found in ANDA submissions” (see IPQ “Monthly Update” Nov./Dec. 2013, pp. 2-15).

OGD has now developed algorithms that it is currently testing and piloting for delayed and modified release products, as well as for topical dosage forms and oral suspensions and solutions.

Raw commented that he worked with Office of New Drug Quality Assessment (ONDQA) Director Christine Moore in the application of FMECA to ANDAs, and that ONDQA reviewers “have also seen the success of this approach and are also starting to employ similar concepts to their NDA reviews.”

OGD’s ANDRE RAW ON THE NEW RISK-BASED PROCESS FOR ANDA REVIEW

At the June Generic Pharmaceutical Association (GPhA) CMC Workshop, OGD Chemistry I Division Director Andre Raw discussed the risk-based review process that OGD has instituted for ANDAs. In his presentation, Raw covered: ● the drivers for the new risk-ranking approach ● how OGD’s QbR and QbD efforts helped inform it ● how it was developed ● how it works ● the success to date, and ● future plans.

Why did we decide to do risk-based reviews? Well, there are various reasons:

First of all, when we were in the GDUFA negotiations, there were various assumptions made – one was that applicants would withdraw their applications now that they had to pay for them. But I am not sure if that assumption really came to fruition.

An additional assumption that was made was that the maximum number of applications we would receive, based upon historical projections, would be 700. From my understanding, we received well more than a thousand per year – greatly above the maximum threshold that we anticipated.…

This sort of sets the foundation of why we are doing a risk-based review and implementing quality risk-management (QRM) procedures into our office.

As we all know, we have the applications coming in, and we have the GDUFA timelines that have been set to begin in October of this year. We have to make sure that we have adequate resources to make sure we meet these goals, but at the same time make sure that the generics that we do approve are really high quality generics.

We do not want to meet timelines just for the sake of meeting timelines. We are going to meet the timelines. But we are also going to make sure – and this is more important – that the products are of very high quality and all of the risk factors are addressed.

QbD Impact and Competing Priorities

I think [CDER Director] Janet Woodcock mentioned the concept of the desired state. It is ‘a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.’

Based upon the 21 \textsuperscript{st} century initiative, from this vision from Janet Woodcock came the concepts of quality by design (Qbd). There were various guidances that brought to light these issues.

The first one, obviously, was ICH Q8, and also the guidance for industry on process analytical technology (PAT). At that time it was mainly geared for new drugs. But at the same time, around 2005, we started developing the question based review (QbR), in which, for the first time, we started asking for pharmaceutical development information from ANDA sponsors. That was our first step toward implementing the quality-by-design initiative and capturing Janet’s vision of
the 21st century for pharmaceuticals.

Then, in 2011, we developed QbD examples for ANDA products – both the immediate release [IR] and the modified release [MR] examples. The problem that we met with the ICH Q8 guidance is that it is very high level. So the question was, ‘what does QbD really mean?’ It is a very abstract concept. It is almost a philosophical concept. So we spent a lot of time trying to illustrate to the generics industry what we mean by quality by design to provide more transparency as to our expectations of what QbD is all about.

I guess the question that we all ask ourselves is, ‘do we really have competing priorities?’ We have the chemistry divisions in the Office of Generic Drugs [OGD]. We obviously have our GDUFA backlog. And we have to meet our GDUFA goals. So that is one competing priority that we have. But with concept of QbD in the picture, now we are receiving an explosive amount of QbD information that we never really received before from ANDA applicants. As a consequence, not only did our submissions become bigger, but our reviews also became much bigger.

It seems like we have two opposing forces here: How are we going to make sure that we can ensure the high quality pharmaceuticals and implement the QbD concepts as well as meet our ANDA backlog and GDUFA goals?

Is there a real contradiction here? In my opinion there is no contradiction at all. Because one concept of quality by design that I think was alluded to a little bit in the IR and MR examples is the concept of quality risk management. I can see that since we started this journey of understanding QbD we have been learning a lot. We started with the question based review. We got the IR and MR examples. Actually the IR and MR examples themselves do illustrate some of the concepts of quality risk management. As we are going through this journey…we are truly understanding what the meaning of QbD really is. I think this is the next step in our implementation of QbD and making sure that the vision of 21st century is carried out.

Understanding Failure Modes and Mitigating Risks

Before I talk about quality risk-management, I want to take one step back to talk about what we really do in our ANDA review from a very high level. To me it is divided into two parts conceptually.

The first part is product standards and methods. Basically we set product standards. This is purely specifications – specifications for potency, specifications for the solution itself. That is one part of our review.

But there is another important part of our review, and that is the concept of understanding the potential failure modes of the product designs and whether or not the sponsors have, based upon their design and manufacturing process, mitigated those risk factors in terms of the formulation. This really requires a really in-depth understanding of the formulation and process design. We are all set to do that because we have hired the top formulators and the top chemical engineers from the industry to help us carry out this mission.

It really requires that in-depth understanding: What are the risk factors associated with that formulation? What are the failure modes? And how have you as the applicant addressed those failure modes? In terms of the manufacturing process, what are the failure modes for your manufacturing process? Have you defined your control space for the critical processes? Those are the questions we are looking for in your applications, in which QbD plays a very integral role.

I think a nice example is content uniformity. All applications, regardless of risk, have the USP <905> standard for content uniformity. But different applications have different risk potentials of not meeting that particular standard. So, obviously, for high-dose drugs, the risk of not meeting that standard is very low. Conversely, for low-dose drugs, where there is a lot of segregation potential, the risk of not meeting that standard is very high.

Therefore, based upon QbD principles, it is very important that you demonstrate an understanding of the segregation potential based upon your understanding of the material properties of the input materials that are used, the critical process parameters that are used in the blending, as well as the sampling scheme that you use to ascertain whether or not you met that particular standard for content uniformity.
Really there are two conceptual parts to this – standards and risk identification – and determination whether those risks were mitigated by the design, formulation, process, and sampling scheme.

**Quality Risk Management**

This is where I am going to get into the concept of quality risk management. When we do risk assessments, we have three factors:

- The first factor is **patient risk impact**. Obviously it is very high for NTI [narrow therapeutic index] drugs. It is very high for immunosuppressant drugs. That is one factor to determine in terms of severity of the consequences of failure to the consumer.

- Another factor is **probability**. Obviously, for more complex products the probability of a failure is higher than it would be in the case of a simple product. A low-dose formulation in which there is a high potential for segregation obviously has a higher probability of failure than one that has high-dose, and so forth.

- The third concept, in terms of our risk assessment, is **detectability**. If you do have a product that is not of good quality, we want to make sure that we have appropriate detection procedures to ensure that those substandard products do not reach the consumer.

So, if you have a low solubility drug or extended release formulation in which you do not have bio-relevant dissolution, the detectability of that failure mode is low. If you have IVIVC [in vitro in vivo correlation], your detectability of that failure mode occurring and preventing it from reaching the consumer is much higher. Actually [the scores are] the inverse. So basically if you have an IVIVC your detectability score would be one. If you do not have a bio-relevant detectability, your score would be five.

The concept that we laid out is that we would take products and rank the risk based on particular product CQAs [critical quality attributes]. The concept is that if the CQA is really a low-risk one, based upon our risk assessment, there really should be minimal discussion of risk mitigation. Often times simply discussing that the product meets the typical product standards could very well suffice.

Then comes the in-between – which is the yellow – in which we do have some moderate risk. So there probably should be some limited discussion of that risk mitigation.

Then, of course, comes the case of very high risk. The idea is that reviewers in our submissions are expected to critically evaluate the formulation design, process, and sampling to ensure that that drug risk is mitigated. It is important that that is the expectation that we have right now in our reviews.

Just to give you an example – to simply state that your product meets a product standard of dissolution, or USP <905>, does not mitigate that risk. All it says is that it has that standard, but it does not mitigate the risk of it not meeting that standard.

Basically, the expectation is that reviewers – the formulators and the chemical engineers that we hire – provide a discussion of how those risks were mitigated based upon the information that was submitted in your application. In those cases, the expectation is that we would hope to see this information in the application. Obviously if we do not see this information we would have to issue deficiencies.
Risk Ranking of Products by CQAs

How do we rank products? How do we determine if something is low, medium, or high risk? The first thing that we did started more than a year-and-a-half ago. It became clear to us that we needed to do these risk assessments because what happened was, like I said, with all the QbD information, reviewers were spending a lot of time on applications that were really low-risk. They were looking at all the QbD information for these low-risk products. And I was asking, ‘why are you doing this?’ Conversely, we had complex applications and we had reviewers that were potentially not adequately addressing the high-risk issues.

So, in order to circumvent that, we decided to have some very important [agency personnel] involved. I was involved within it. My deputy director Bing Cai was involved, and also [OGD Reviewer and QbD Liaison] Danny Peng. We did a preliminary risk assessment for every single ANDA in our division….

We performed a preliminary hazard analysis [PHA], in which we took into consideration the severity of effect based upon quality failure times the probability of effect based upon principles of the manufacturing process and formulation design principles. For example, if you use an amorphous form, obviously the probability effect is much higher than if you used the more stable crystalline form, and so forth.

We rated these attributes based upon low, medium, and high, for each of the CQAs. I think the expectation that we laid out to our division head was that we should review the product in-depth commensurate with the risk factor.

This is just one example: This was actually from one drug. Basically there were three CQA risk factors that we identified that I am going to list for you…. What happened was that every single ANDA had a preliminary risk assessment that myself, Bing Cai, or Daniel Peng, did. We used that risk assessment to guide us through the first thing that we should do – look at the risk assessment table and then review that commensurate risk.

For one product, the risk assessment said content uniformity was the highest risk. So basically, for the reviewer, just do not say that USP <905> is enough to mitigate that risk, because it is not enough. We definitely need to ensure that the sponsor understands the material properties that may impact segregation.

Alternatively, if the sponsor does not do that, they have to do a much more extensive sampling strategy, because we know that, for this type of drug, just sampling ten units is not going to be enough – it has a very low detectability. We know that just because ten samples passed does not mean that the rest of the batch [of] tablets [would pass]. So they would have to do more extensive sampling. That was the expectation that we laid out to the reviewers.

That is really based upon good science and concepts. Similarly, the bioequivalence risk was deemed medium. And in that case, it was a low solubility drug by the BCS [biopharmaceutics classification system]. But then the reviewer mitigated this risk by saying, ‘look, it is a low solubility drug by the BCS. However, it is high solubility at pH 1.2 and 4.5, though it is low solubility at pH 6.8.’ Basically the reviewer was able to mitigate that risk by saying that as long as that tablet dissolves within 30 minutes, the drug should be dissolved and bioavailable through the GI tract. So that would mitigate that risk.

The third thing was that we knew the product is as stable as a rock. So you do not have to look at how the sponsor designed the formulation to be stable. All we had to do was ensure that it met the stability specification. So long as it met the stability specification we felt that that would be sufficient, because we knew that the inherent properties of the API rendered it to be very stable. So we did not have to have a complete understanding of how the sponsor developed the formulation to mitigate those risk figures. This is just one example, and there are many of them.

Risk Program Expansion

We did this for about a hundred ANDAs in our division. It was a tremendous success. I think it really helped the reviewers focus on where the risk factors are. Even though a sponsor would submit a tremendous amount of QbD information on a factor that was probably low-risk, they would not have to document so much on it. But they would have to document a lot on the high-risk area. The reviewers really liked this.
We did this for our division. It was a very big success. The pros of it were that it was a semi-quantitative analysis based upon probability and severity from a quality perspective, and definitely it was a power enabler of risks based upon product specific CQAs.

It really focused on the hot-spots of the formulation that were high-risk, so that we could make sure that those were addressed. Because the important thing is that we want to make sure for the high-risk products that we approve, the risks have to be mitigated prior to the final approval.

The cons, of course, are that this is highly dependent on the risk assessor’s prior knowledge and experience, because people may have different opinions, and that could be a big problem. That was something that we were very concerned about – that this could pose a lot of problems in terms of widespread implementation as a regulatory risk assessment tool.

But fortunately, at the same time that we are doing this and it was going smoothly, Christine Moore from ONDQA [Office of New Drug Quality Assessment], my colleague, was also doing something very similar. She was developing a quantitative, objective system of rating risk based upon failure mode, effects and criticality analysis [FMECA]…. It is a little bit different from the PHA. There are many risk assessment tools, but she decided to use the FMECA approach, where one calculates a risk priority number based upon the severity to the patient. It can go from a scale from one to five – the probability of occurrence based upon formulation design and manufacturing process principles, and probability of failure based upon typical detection strategies that are employed during manufacturing.

There are many advantages to this. But one particular advantage that we like, of course, is that it focuses on the risk to the patient because it takes into consideration the severity of harm. The other more important thing is that it is more objective – we actually have a system by which we can score.

For example, if you have a more stable crystal form, we have a score for it. If you have a metastable form that can transform, we have another score. If you have an amorphous form, we have another score. If you have this drug load, you have one score. If you have a distribution method that is not bio-relevant, we have another score. So we can score everything. We can do it objectively, independent of opinion. Actually, we are even thinking about computerizing this thing….

We realized that we wanted to implement it. So we took our approach and modified the algorithm to see if it would align with our PHA scores. Out of a hundred ANDAs, I took about twenty examples, and we developed the algorithm to see if our [ranking] would fit with our initial PHA assessments, which are more subjective. These are just two examples (see box on p. 9).

One was a low-risk product. And you can see, based on the algorithm that we modified, we could actually come up with the exact same score as our subjective PHA assessment. Similarly for the high-risk product, we could do the same thing.

We did this for twenty products and we felt that we had a very good system in place to rate products based upon the risk. We were very happy about this.

We then did this for about 350 solid oral dosage forms that are pending review. This, sort of, gives you an idea of the risk profiles of various products (see box at right). It is a little bit on the conservative side. But keep in mind we are an agency. We have to be a little bit conservative. The government is a little bit conservative.
**PHA and FMECA Risk Ranking Methodologies Compared**

The following are two examples of comparisons OGD performed that show that the PHA method it initially employed produced similar scores to the FMECA method it switched to. The first one is a low-risk product; the second is high-risk.

<table>
<thead>
<tr>
<th>CQA</th>
<th>Probability of Occurrence (O)</th>
<th>Severity of Effect (S)</th>
<th>Detectability (D)</th>
<th>FMECA RPN</th>
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<td>D1</td>
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</table>

Basically, about 45% would be medium risk and about 36% would be high-risk. This kind of study also told me that this sort of system does, to some extent, provide a realistic assessment of product risk based on various CQAs, at least in the initial risk assessment. I remember people sometimes saying that IR products are all simple and modified release products are all complex. That is not true. We know if we get into the nitty gritty details that some IR products are super complex and we know some MR products are very simple. This really gives us a very balanced view of the overall risk.

We did this for 350 products and ran it through our division.... Then we started piloting this with the immediate release products – not only within my division, but all the OGD chemistry divisions.

We have data showing that, especially for the low and medium risk products, it really does increase the efficiency of our review. For the high-risk products, it really focuses the reviewer on the high-risk elements. So it was a tremendous success. Every single IR product that you submit will a get a score right now.

Based upon the success, we decided to expand this to other dosage forms. We have developed algorithms, which we are currently testing and piloting, for the delayed and modified release products. We are also doing this for topical products.
dosage forms, based upon the design characteristics, as well as oral suspensions and solutions. I can say to you that some of those algorithms are quite elegant – they really take into consideration the design principles of the formulations. We are very happy with these algorithms so far.

**Risk Management Formalized**

Risk management is now formalized in the ANDA annual review. I can tell you that every single IR product that is reviewed has an initial risk assessment using this algorithm. It tells us what the initial risk is, and that will help focus the reviewer on the areas of high-risk. Then conversely, if there is a not very high risk, then they do not have to spend that much time on it. After this review, the reviewer is expected to provide an update to the risk ranking based on their assessment of the application.

I also wanted to mention that this is an initial risk assessment that takes into consideration fundamental properties of the API, biopharmaceutical characteristics, your manufacturing process, and so forth. Obviously it cannot be perfect. But it gives a very good start. I will tell you that probably about 85-90% of the time it is right – it is right on the money. Then 10% of the time it may be a little bit inaccurate. It is very hard to be perfect without looking completely at the application.

During the review of the application if they find an area that is of high-risk, they can always elevate. So we feel that this is a very good method to review applications.

Like I said, what I can tell you is that this has really been a success within our office. And it looks like not only is this being employed by ANDA reviewers, but new drugs are also following suit. The NDA reviewers have also seen the success of this approach and are also starting to employ similar concepts to their NDA reviews.

**Conclusion**

The conclusion is that with implementation of QbD, sponsors are still expected to provide the complete product development reports to ensure a robust formulation and manufacturing process. You are still required to provide that information. There is still that expectation from us.

This tool, in my opinion, is just part of the journey in our implementation of the 21st century quality initiative – it is just a natural progression of that.

Formal risk management approaches will be used in ANDA reviews to ensure that the high-risk areas receive appropriate scrutiny and really to make sure that we are not going to miss anything big. That is really good. We cannot miss anything big. If we miss anything big, that is really bad. We cannot afford to do that to the American consumers. So, really it is a very powerful tool.

Formal risk management will also streamline the review for lower risk areas to ensure review timelines under GDUFA, and we actually have data showing that this is really the case.
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A draft guidance on the content and format of abbreviated new drug applications (ANDAs) is the most recent effort by the Office of Generic Drugs (OGD) to clarify and streamline the ANDA process and facilitate the implementation of the Generic Drug User Fee Act (GDUFA). The draft was released in mid-June for a 60-day comment period.

In May, OGD released a Q&A guidance that is intended to clarify the June 2013 ANDA stability guidance.

Also in the pipeline nearing release are draft guidances on ANDA: • amendments • supplements, and • controlled correspondences under GDUFA.

The new 32-page ANDA submission draft outlines the expectations for each section of the five CTD modules: • administrative information • CTD summaries • quality • nonclinical study reports, and • clinical study reports.

An appendix lists the 31 FDA guidances referenced in the draft that are also intended to assist in preparing an ANDA. A second appendix shows a suggested template for the cover letter that needs to accompany an ANDA submission.

The guidance does not address the fee structure or payment of obligations under GDUFA, the submission and assessment of drug master files (DMFs), amendments to original ANDAs, or, changes being effected (CBE) and prior approval supplements.

At a Generic Pharmaceutical Association (GPhA) CMC Workshop in early June in Bethesda, Maryland, Office of Generic Drugs (OGD) Acting Director Katherine “Cook” Uhl provided an update on current guidance efforts and the “huge” impact GDUFA is having on the agency and the industry.

Uhl highlighted a January Federal Register (FR) notice requesting industry input on ANDA submissions, which helped in the development of the June draft guidance.

The January FR notice asked for comment on: • ways to improve the quality of ANDAs and associated amendments and supplements • the difficulties sponsors are having developing and preparing their ANDA submissions, and • suggestions that will improve the completeness and quality of submissions. Also included was a list of common deficiencies that agency reviewers have seen in ANDAs (see below).

Uhl commented that half of the 14 responses “were on topic, and half of them were off topic.” The on-topic ones “were pretty much what we were looking for, including: • general concerns and questions about the application content • questions about the inactive ingredients database • requests to us for more summary templates to help you in putting your applications together, and • kind of a plea to us for consistency in how we provide deficiencies and review standards and feedback.”

She also acknowledged a white paper that GPhA put together on ANDA submissions, which she characterized as “very helpful.” However, she cautioned that the paper is “very specific to CMC quality,” pointing out that there are “components to application quality that are larger than just the CMC portion.”

**COMMON MISTAKES SEEN BY OGD REVIEWERS IN ANDAS**

**Filing:** Failure to provide a completed Form FDA 356h; unjustified inactive ingredient levels; inadequate dissolution data; packaging less than the recommended threshold amount without justification; inadequate or insufficient stability data; submissions of non-qualitative and non-quantitative (not Q/Q) same formulations; electronic submission and formatting deficiencies; applications containing an incorrect or unfounded basis of submission.

**Chemistry:** Poor or inadequate justification of impurities limits; failure to provide a list of potential impurities and their origins; failure to provide adequate verification of analytical procedures for active pharmaceutical ingredient and finished dosage forms, where appropriate; failure to identify the critical manufacturing process parameters or to link in-process controls to development studies; failure to provide appropriate acceptance criteria of manufacturing yields for the critical steps, or providing yield values varying without adequate rationale or explanation.
Stability Q&A Benefits Highlighted

The 14-page Q&A on stability for ANDAs released in May answers a series of questions in five areas: ● general ● DMFs ● drug product manufacturing and packaging ● amendments to a pending ANDA, and ● stability studies.

At the June GPhA meeting, Office of Pharmaceutical Science (OPS) Acting Chemistry Deputy Director Susan Rosencrance characterized the 2013 stability guidance and accompanying Q&A as a “program enhancement” that “will really benefit all of us in the long run” (see box below).

Benefits of the Stability/Q&A Guidances

At the June GPhA CMC Workshop, OPS’ Rosencrance provided “the five biggest benefits” she sees coming from the stability guidance and Q&A:

● The first is that after many years we now have formal guidances with clear recommendations on what our stability expectations are. For so many years we got so many questions that required us to address them and took our resources just because there were no formal guidances available.

● We now have a formal process for generic drugs. It aligns with the ICH guidances. This is one of the things that some people had wanted.

● It brings us closer to harmonization with stability recommendations for new drugs.

● It also harmonizes with other generic programs globally in Europe and Japan.

● And overall it enhances the quality of generic drugs. Over the last five years with products becoming more complex, we kept seeing more and more problems associated with stability failures and recalls. Just having this additional data gives assurance that your product can stand the test of time.

She acknowledged that the new stability recommendations are a “huge change” for industry, and pointed to agency efforts to help the process “go smoothly.” These include a small business webinar held in November 2013 focusing on the June 2013 guidance and a second webinar in June 2014 that focused on the Q&A. The webinars provided an opportunity for smaller domestic and international pharma companies to learn about the two guidances and pose questions to FDA staff.

Rosencrance also noted that the agency has held training sessions for OGD filing and chemistry reviewers to ensure that they are clear on the stability recommendations in the two guidances.

Sharp Rise in Controlled Correspondence

OGD’s forthcoming draft guidance on controlled correspondence will follow in the wake of a sharp rise in those correspondences – specifically the ones containing chemistry questions.

Rosencrance explained that while in the previous ten years chemistry-related correspondences comprised between 2-8% of all OGD correspondences, “for reasons we are not quite sure of” that number has doubled to 16% in the last year.

To address the surge, OGD put in place a centralized, dedicated small group to manage the chemistry-related controlled correspondences. It consists of two coordinators, three to six primary and secondary reviewers, and one sign-off authority.

Since December, the group has “done a lot” to clear out the backlog of controlled correspondences. There are still 90 that are pending, 90% of which were received in 2014. The
goal is to reach a steady state – where the number coming in and those completed are equal – by October of this year.

The OPS official stressed that correspondences could be improved by being more specific and concise.

“If you put a question in that impacts many disciplines, it makes it much harder to deal with,” she emphasized. “It would be better if you kept it to one discipline.” She also noted that FDA has a web page with advice on submission of controlled correspondences.

**DMFs Must be Available for Reference at ANDA Filing**

Also at the GPhA meeting, OGD DMF reviewer Ramnarayan Randad offered advice on submissions for active pharmaceutical ingredients (APIs).

He reminded the attendees that beginning in October 2014, DMFs must be “available for reference” at the time of ANDA submission or the ANDA will be categorized as “refuse to receive” (RTR) (see *IPQ “Monthly Update”* Nov./Dec. 2013, pp. 16-27).

For FY 2013 and 2014 this was not the case. DMF holders had the entire ANDA filing window for the master file completeness assessment to be performed. With the new timing requirement, the agency recommends that firms coordinate the DMF fee payment and ANDA submission to allow the DMF to pass the completeness assessment prior to filing the ANDA.

Randad also provided “suggestions” on how to avoid a DMF-related RTR (see box below).

**DOWNLOADS FROM THE STORY:**

- FDA 2014 ANDA submission draft guidance
- GPhA White Paper on “enhancing ANDA submissions”

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**How to Avoid an RTR Due to DMF Deficiencies**

*At the GPhA CMC workshop, OGD’s Randad provided the following suggestions on how to avoid a “refuse to receive” (RTR) status for an ANDA filing due to problems with the referenced DMF:*

- Make sure the DMF is on the “available for reference” list prior to the ANDA submission.
- Communicate with the DMF holder so they know the ANDA submission timeframe.
- Pay the DMF fee six-months in advance of the planned ANDA submission date. This will allow sufficient time for two cycles of completeness assessment review, if needed.
- Submit a high-quality DMF – preferably in eCTD format.
- Know if the DMF is eligible for an administrative completeness assessment.
- Make sure the choice of starting materials is appropriately justified.
- For older DMFs, know whether a complete update needs to be submitted, and submit ahead of payment.
- Make sure FDA has the current contact information, e.g. fax number.
- Respond to incomplete letters as quickly as possible – 30 days or less is ideal. Provide notification of amendment as instructed on the fax cover sheet.
- Contact OGD with completeness assessment status requests if the DMF is not on the list or you have not received a “DMF Incomplete” communication (dmfogd@fda.hhs.gov).
Learn how to plan, conduct, and document an audit of excipient manufacturing facilities for conformance to excipient GMP standards as listed in <1078> of USP/NF and in IPEC GMP Guidance. This course will also cover the new expectations in the ANSI Excipient GMP standard that is in final review.

**Workshop Overview**

- Assessing GMPs for Excipient Manufacture
- Where GMPs Begin
- Audit Planning
- Pre-audit Questionnaires
- Alternative Audit Approaches
- Audit Checklists & Techniques
- Necessary Auditing Interpersonal Skills
- Defining Pertinent Audit Issues In Observations
- Writing & Rating Observations
- Excipient Manufacture Requirements vs. APIs
- Review of the ANSI Excipient GMP Standard
- Hands-On Mock GMP Audit

**Workshop Content**

This is a comprehensive workshop in excipient auditing for makers and users. Training will analyze the essential elements of excipient good manufacturing practice for materials intended for use in pharmaceuticals or dietary supplements.

The workshop will focus on excipient GMP compliance and attendees will learn auditing techniques, report writing, observation classification, and other topics that relate to the manufacture of excipient ingredients. The workshop contains exercises to hone observation skills, including participation in a hands-on mock excipient GMP audit. Participants will gain a thorough understanding of risk-based excipient auditing and learn how to assess whether an excipient GMP quality system can achieve a satisfactory level of compliance. Finally, attendees will learn how to differentiate the requirements for excipient manufacture from those of APIs.
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IPEC and IQ Consortium Team Up to Push for an Independent Pathway for New Excipient Review

A call to action is reverberating through the pharmaceutical community for the establishment of a viable regulatory pathway for new or modified excipients, which would empower industry to develop more quality-by-design-based formulations.

Picking up the mantle from the industry side are the International Pharmaceutical Excipients Council (IPEC) and the IQ Consortium, who are working together to develop a proposal for the pathway that will be compelling to FDA.

An independent FDA safety review system for excipients that would foster their being designed and/or adapted to meet the increasingly-sophisticated demands of formulating pharmaceuticals has been an objective of IPEC’s since its formation two decades ago.

In turn, the frustrations of pharmaceutical manufacturers of not having new excipients in their formulation toolbox has forced the concern onto the front burner of the IQ Consortium, formed to help “advance science-based and scientifically-driven standards and regulations for pharmaceutical and biotechnology products” (see IPQ “Monthly Update” June 2012, pp. 31-38).

The dimensions of the problem created by the lack of a pathway for new and co-processed excipients as well for their use in strengths that exceed that listed in FDA’s Inactive Ingredients Database (IID) were articulated by a panel of experts at a session of the IPEC ExcipientFest conference in late April in Raleigh, North Carolina.

Included on the panel was representation from excipient manufacturers Colorcon (Regulatory Affairs Manager Chris DeMerlis) and BASF (Pharmaceutical Ingredients and Services Marketing Head Nigel Langley), excipient users GlaxoSmithKline (Product Development Director Vinod Tuliani) and Boehringer Ingelheim (Pharmaceutics VP Keith Horspool), and an industry consultant (FinnBritt Consulting Pharmaceutical Sciences VP Chris Moreton). The panel was moderated by Pharmaceutical Technology Editor Cynthia Challener.

The panel discussion encompassed a wide range of excipient manufacture, supply and use issues that are impacted by the current regulatory paradigm. In focus were the related economics, formulation science impacts, market needs, incentives and risks, as well as efforts under way to address the problems.

Not Designed for Purpose

Most excipients currently in use in drug products were originally made for the food or cosmetic industry – reflecting in part the high review and approval hurdles facing excipients designed specifically for pharmaceutical products, which would be more fit-for-use.

Similarly, currently-approved pharma excipients proposed to be used at higher levels, while not getting the same level of scrutiny as completely new excipients, still require a safety review that can take months – effectively dissuading especially generics firms from considering them for their formulations.

When a drug product using a new excipient is approved, the IID is populated with the level used in that drug formulation, BASF’s Langley explained at the IPEC session.

“So, as it stands, when a company wants to produce a drug formulation that contains a higher quantity than is actually listed in the IID, by definition that is a new chemical process, which then has to be tested for safety.”

Under the current paradigm, new excipients and new uses or levels of existing excipients only gain agency attention for a safety assessment when submitted as part of a drug application.

That represents an issue for excipient manufacturers, because “nobody wants to be first in this industry,” FinnBritt’s Moreton pointed out. “We are very conservative.”

Co-Processed Excipients Also Implicated

“Novel excipients” also include those manufactured by co-processing already-approved excipients to produce a product with superior functional properties. For these, additional analytical data will be required to show that new chemical entities were not introduced as a result of the manufacturing process.

Co-processed excipients are not simple mixtures and therefore must be considered a unique entity on their own. When these materials are used for the first time drug, companies can be concerned about approval delays.

“It would be a very brave pharmaceutical executive who would risk a potential new blockbuster on an unknown, untried, untested excipient,” Moreton emphasized. “It requires a lot of guts and a lot nerve, and, shall we say, blind luck in some cases…. It comes down to fear of the unknown – the unknown in this case being what the regulator will say. So people are very wary of new excipients.”

However, he pointed out that “it has been done. Cydex did it with a modified β-cyclodextrin [sold under the trade name
Captisol]. It took a lot of guts…. They took a chance because they had a known technical need, and that drove it.”

Moreton explained that the cyclodextrin example took place “at a time when we had a lot more money and a lot more commitment to relatively high risk scenarios. Those days are gone.”

He also stressed the importance of developing an improved process that would allow “an independent approval of these materials,” where all types of new or novel excipients could be assessed for safety by FDA prior to when the excipients are utilized in a drug formulation.

“We do not want to file an NDA for a compound that might fail and then have to restart all over again,” Moreton emphasized. “That is just not viable.”

Better Products for Patients at Issue

Although the current approval pathway is serving as a roadblock to new excipients being developed and used, panel members from both the excipient manufacturer and user sides stressed the need for new excipients and the positive impact they would have on the development and delivery of new drug product formulations.

Moreton commented that “more excipients would give us more options, and perhaps give us more viable products. And that is important.”

GSK’s Tuliani echoed the point: “With the new compounds that are coming through the pipeline, we need to make sure that we have more options available to make sure that we can get the drugs to the patient. At the end of the day, [our focus] is the patient. And the more options you have, the more confident you feel.”

Also representing the pharmaceutical company point of view, Boehringer-Ingelheim’s Horspool further emphasized the positive impact new excipients could have on the patient.

“There are number of things that we believe we could improve with better materials,” he said, including biological formulations where he sees a “huge opportunity.”

“We do not want to give daily injections to the eye, for example,” Horspool stressed. “We want to have things that act longer. So we need materials that can help us deliver these drugs over a sustained period. There are a whole series of opportunities and we are just not meeting enough of them given our current excipients.”

Also regarding the importance to patients, Langley emphasized “what is compelling this afternoon [is that] the patient will suffer. And that is something that we really have to put into this equation and mix as well – not just the interest of the excipient companies or the pharmaceutical companies. The end result is better patient care and better medicines to treat diseases.”

Horspool agreed and added that it is important to consider “the risk of not having these materials with respect to supplying product to patients.”

Speaking from an excipient maker’s vantage point, Colorcon’s DeMerlis pointed out that “the need is evident. For new chemical and new drug entities [NCEs and NDEs] we definitely have bigger needs now than we have ever had. And there are bigger opportunities.”

Moreton emphasized the importance of communications between excipient makers and users in filling the new excipient needs.

“The first thing is to try and get some consensus in the pharma industry around what it is they actually want,” he explained. “What are the types of materials that we all want and for what applications? I think we have left it up to excipient vendors to try and second guess our needs, and that has not always been, when push comes to shove, the materials we actually wanted and were willing to stand behind.”

Development Incurs Business Risk

Although the panelists agreed on the need for new excipients, they also acknowledged the business risk excipient manufacturers incur when developing new materials.

BASF’s Langley addressed the problem from an excipient manufacturer’s perspective. “I think we are at somewhat of a crossroads here. Because clearly there is a market need for new excipients and new materials. But the challenges for companies such as BASF and others to develop modern excipients are really high.”

Langley stressed that the development process “takes a number of years before you actually have the product launch.” He compared and contrasted excipient and API development.

“When you think about the actual drug cycle and the development of new chemical entities such as an API,” he said, “it is not too dissimilar when you are looking at an excipient as a new chemical entity – the only difference being that when we launch a product as a new excipient, then we have to start to entertain and have interest from the pharmaceutical community to actually test it. So there is
no return on the investment when you launch an excipient, unlike a drug product.”

He pointed out that “the burden is placed completely on the excipient company to actually manufacture and support its investment,” which may not be realized for 15 years. “That is a challenge in this culture where we are looking for quicker returns on investment.”

Bl’s Horspool commented that “we take and carry an awful lot of risk…. We need to make sure that the regulators understand, and pharma knows how it can help. I think that has been one of the problems.”

Langley stressed that the current approval situation jeopardizes the availability of new excipients in the future and deserves front-burner attention.

“I think there is a need to do things very quickly,” he stressed. “Because if we do not do that, we may find that we will not be able to have that conversation in the future.”

Excipient companies may “make a decision internally not to support novel excipients in the future. That is the risk if we do not have the opportunity to entertain discussions with the agency – to have discussions that make sense with respect to an industry view and [get] their feedback on options.”

Review Process Would Spur New Excipients

IPEC’s longstanding effort to help develop a separate approval pathway for excipients that would speed their approval and decrease the risks to both excipient manufacturers and users is being bolstered by joining forces with the IQ Consortium to pursue this common goal.

The IPEC/IQ partnership, Langley said at the late-April meeting, “is something that we are putting together. We are putting down background documents between the two organizations. It has not been finalized yet, but the intent is to do that and then start to have some dialog – hopefully within the next couple of months.”

FDA’s IID working group – which IPEC has participated on – is viewed as a potential forum to put together an approach that is similar to the one being examined for families of excipients.

The idea is to create a package of safety information that would include all the appropriate information presented in a standard way, which would be reviewed and approved independently of an NDA or ANDA by FDA.

If an independent review process for excipients such as this was in place, Colorcon Regulatory Affairs Director and IPEC past chair Schoneker commented to IPQ, “a lot of major excipient companies like Colorcon, BASF and others would probably be coming out with many new excipients, which would be very useful to improve drug development. All of a sudden there would now be an advantage for an excipient manufacturer to actually bring forward a new material.”

In line with the discussion that took place at the IPEC conference, Schoneker explains that “almost nobody is looking at developing a brand new excipient these days, because there is little guarantee that you are going to get acceptance in the marketplace or if any customers will ever try to use the material in a drug application, regardless of how good the excipient might perform. And if you do, it is going to be fifteen years down the pike because of the current cumbersome approval processes that depends on a drug company being a guinea pig for the first use of the excipient, which can be risky.”

During the Q&A after the IPEC meeting panel discussion, Schoneker cited FDA’s desire for innovation in drug products, and stressed that “the real driver that is going to get excipient companies to come up and do the toxicology work that is going to be required and actually come up with the new materials and try to get the engine running is innovation. If we have no pathway for getting an approval process independent of the drug application, that innovation is dead.”

The “only way” to get excipient companies to invest in the development of new excipients, Schoneker maintained, is “to have a defined pathway that allows excipient companies to say, ‘if I invest 5 million dollars in toxicology studies, then I can actually go and try to get some sort of independent review where my customers will not be afraid to try it.’”

Langley commented that even if a separate approval pathway is developed, there will still be intellectual property issues that will impede excipient development.

“If we have an approval for an excipient, what we do not have is the extension of patent life,” he explained. “Now if you do the math, you end up with about two years of patent life left by the time you have gone through all the development of a new product, assuming you get a good uptake very early on.”

If the product is successful, then “there will be imitators…. So we have to solve the issue, not only of the approval process, but also intellectual property, because without that it is not viable.”

The Time is Ripe

Langley and Schoneker made a strong case for why the time is ripe to push forward with discussions regarding an independent agency review process for excipients.
“We sense collectively that the time is right to have that type of discussion,” Langley commented. “We sense that it is the opportune time to make that discussion work. Because if we leave it longer, for a few more years, then there may not be the interest from either party to do that.”

Schoneker, a founding member of IPEC in 1990, explained that one of the association’s “key missions” at its inception was to come up with an independent review process.

“It is now 2014 and we are still talking about how we get started,” he said. “That is unacceptable. We have to make it unacceptable. We have to drive it forward and take no prisoners. And we cannot let past history stand in the way. I think that is where we are today.”

He stressed that “IPEC and IQ are going to do it. We are going to make this an issue. We are not going stop until we have a process.”

FDA, Schoneker commented, is “very interested in hearing what we have to say.”

“There seems to be an openness with all of the…new thinking” at the agency, creating an environment that is “more open to this type of discussion than I think there ever has been before.”

“There are demands for more excipients for pediatrics. That is a good hook. We have quality by design. That is needed. And we have all of these unmet needs with new drug processes. If there ever was a time, now is it. Stay tuned. We have a lot of things we are working on. But we cannot take ‘no’ for an answer this time. There has to be a way to work this out. We are not going another 24 years.”

During the Q&A, FDA Office of New Drugs Quality Assessment (ONDQA) Senior Review Chemist Jeff Medwid expressed support for the review of new excipients.

“I would love to see new excipients,” he stressed. “You have something new? I would love to see you bring it in. I would love to review something new instead of the old stuff we have gotten before.”

After filing an IND, he said, “call us up. And if you want to have a meeting, we can discuss the information in your IND. Put three or four permutations together with the three or four new excipients you have, and we will evaluate it. Come and talk to us. I think we are very open…. Hopefully you get the message that you can talk to us any time. I think we are very receptive to new excipients.”

IPEC Sets Up Evaluation Panel to Facilitate Approval Process

Colorcon’s DeMerlis explained that in an effort address the problem, IPEC set up a “new excipient safety evaluation panel” approach for the evaluation of new and co-processed excipients. The process uses expert toxicologists on the panel to provide an assessment of the safety of an excipient for a particular intended use and exposure level.

IPEC describes its “independent new excipient evaluation process” as designed “to help reduce the cost and uncertainty related to use of novel excipients in pharmaceutical formulations, thereby encouraging their use in drug development programs and encouraging drug formulation innovation.”

Schoneker cited an example of a co-processed excipient his firm developed “several years ago,” which was one of the early excipients to be taken through the IPEC panel’s review process.

The excipient involved is a co-processed material made from cornstarch and pregelatinized cornstarch that has “unique properties” and has received “very positive feedback from customers.”

The IPEC panel supported its use at the level the firm recommended and provided a report that Colorcon can supply to customers as well as to FDA to support the safe use of the material.

The panel report is very useful in helping to minimize the uncertainty that pharmaceutical customers should have when using excipients such as this. However, Schoneker explained, it has become clear that many pharmaceutical companies still would prefer to have a safety assessment done directly by FDA before they are willing to use a new excipient in their drug products.

Having a regulatory clearance process which involves an independent FDA safety review would facilitate new excipient use, he maintained, and would support the quality-by-design (QbD) paradigm. These types of excipients would be “made for purpose instead of using something that was simply made for the food or cosmetic industry, which may not provide optimal performance in pharmaceutical applications.”

Funding and Staffing Needed for Excipient Reviews

To allow FDA to perform evaluations of excipients independent of the new drug review process, additional funding and staffing would be required.

The combined IPEC/IQ Consortium proposal that is under development will include a consideration of user fees, Schoneker explained.

He noted that during previous discussions between IPEC and FDA, the agency maintained it did not have the resources available to take on the extra work that a separate excipient approval pathway would generate.
Schoneker commented that “generics had this problem, too, with a backlog, and GDUFA is solving that problem to some degree…. I think the key thing is recognizing that resources have to be allocated to get people on the same page.”

The preliminary review process to assure the completeness of Type II DMFs, put in place under GDUFA, could serve as a model for a separate excipient DMF review process.

GDUFA focused attention on DMF completeness. Beginning in FY 2015, the agency will require that DMFs for APIs contain the complete information that the agency wants to see as a criteria for accepting an ANDA for review. The agency will be making public a list of “complete” DMFs to which sponsors will have access. Applications that reference a DMF not on the list will not be accepted for review (see IPQ “Monthly Update” Nov./Dec. 2013, pp. 2-15).

The value to the excipient industry of being able to get the safety data for an excipient in a DMF reviewed independently from a drug application would likely be worth firms paying reasonable user fees to fund the process. In turn, it would spur the development of new excipients designed to enhance drug product quality.

Agency experience with the value of GDUFA, the need to update the DMF system, and the desire to streamline processes and move toward fully electronic systems are forces combining to create a window for implementing an excipient user fee system.

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FDASIA Heightens Focus on Proactive Communications with FDA; Timeliness, Accuracy and Transparency are Key, GMP Compliance Experts Advise

The provisions in the FDA Safety and Innovation Act (FDASIA) for communicating with FDA about manufacturing issues that could play out in drug shortages or facilitate regulatory surveillance are heightening industry’s focus on the agency’s expectations for proactive communications.

Shedding valuable light on these expectations was a panel of experts that convened earlier in 2014 at an ISPE conference on “proactive compliance” in East Brunswick, New Jersey. A session was held at the conference to take a close look specifically at the issues around the communication component in the proactive compliance equation.

The session featured a comprehensive analysis of the FDA/industry proactive communication process by Covington & Burling Partner Jennifer Zachary, whose insights reflected her six-year service between 2005 and 2011 as an associate chief counsel for enforcement at FDA prior to joining the prominent Washington, D.C.-based law firm. Her role at FDA included providing legal advice to the Office of Regulatory Affairs (ORA) and the district offices on field operations, including reviewing warning letters.

Weighing in during her presentation were three other panelists who also played roles in FDA’s compliance operations: two from Genentech’s global quality group – Stephen Mahoney (Senior Director) and Karen Hirshfield (Senior Compliance Specialist) – and Lachman Consultant Services’ Roy Sturgeon.

Long-Term Relationship at Risk

Zachary prefaced her remarks by explaining that she now spends about half of her billable time “either reviewing communications that companies plan to submit to FDA or providing input on communication strategy.... So this is clearly something that companies could be doing more of in-house and getting more effective communications out of their company.”

During the course of her presentation, Zachary addressed: ● the “who, what, when, how, and why” of effective communication ● communication pitfalls, and ● a set of instructive case studies she has been involved with while at Covington & Burling that elucidate effective and ineffective communication strategies. [Editor’s Note: Zachary’s full remarks and those of the other panelists are provided below.]

She explained why completeness, accuracy and transparency are essential in setting up the right communication dynamic between industry and FDA and what can happen when those components are not in place. With intimate experience on both sides, she was able to shed valuable light on how the dynamic plays out and what makes the communications effective.

The communications also need to be actionable – clarifying to the agency the problem and the plan for addressing it, while keeping in view the different constituencies at the agency that may become involved.

Field alerts, biological product deviation reports and recalls are part of the mandatory proactive communication network between industry and the agency, Zachary noted, and these will be joined by “a huge game changer” – FDASIA – with its provisions for preliminary reporting of GMP information that could have a drug shortage impact and for submitting records in advance or in lieu of an inspection.

She went on to explain how a generally proactive approach when manufacturing problems arise benefits a company – “the most powerful one” being the opportunity it gives the firm to “frame the discussion with the agency.”

Genentech’s Mahoney pointed out that adopting the appropriate tone and showing the agency that you understand the problem and are taking steps to address it strengthens the long-term relationship. Zachary echoed the point, commenting further on how “building trust and a good relationship with the agency” plays out to the company’s advantage, such as in the inspection process.

Being upfront when issues arise also opens the door for FDA to provide assistance and give feedback on corrective action plans. Zachary noted that rapid clearance of a change supplement if needed is among the tools in the agency toolkit to “help companies that encounter problems.”

Target Communications at Public Health Impact

A key refrain in Zachary’s presentation, which was echoed by the other panelists, was the importance of understanding that FDA’s primary mission is protecting the public health and that communications need to be framed to assure that the agency understands clearly how they relate to this top priority.

Rather than “throwing the kitchen sink” at FDA, which overtaxes agency resources and prompts further questions, Sturgeon backed Zachary’s emphasis on being clear and
concise about what is important in public health terms.

In discussing her first case study, Zachary reiterated her advice not to overload the communication channels with FDA.

**Common Mistakes in Communicating with FDA**

*In her presentation, Zachary pointed to the following common mistakes companies make in their communications with FDA and explained why they cause problems:*

- waiting too long
- overloading and not organizing information submitted
- making broad, conclusive statements that there is no quality impact
- treating FDA like an expert consultant
- not considering the agency audience and the terms/ acronyms used, and
- not clarifying the public health import.

“The lesson here is to communicate with FDA only when it is going to be useful to the agency and useful to the company,” she said. “Using emails or calls as a CYA [cover your ass] is not a good policy. It is not something your district is going to appreciate. And ultimately it is not going to protect you at the end of the day, because when FDA does get around to looking at what you have done, you remain responsible.”

Another related refrain among the panelists was that FDA is not set up, nor does it have the resources, to play the role of consultant and sort through convoluted submissions and devise CAPAs. “You want to go to FDA with a plan of action and basically ask them for feedback on it,” Zachary stated.

Genentech’s Hirschfield, whose career at FDA included service as a branch chief for CDER recalls, explained how early company contact when there is a potentially serious health or drug shortage impact allows FDA to get its district and review division subject matter experts on board to help resolve issues more quickly and forestall or lessen their impact.

She advised contacting the districts first when GMP issues arise, which have the appropriate mechanisms for “setting the big wheels of FDA in motion.”

**Don’t Forget Calls by Execs**

During the discussion period that followed Zachary’s presentation, Sturgeon voiced his “full agreement” with its content and cited the value of the case studies she presented.

Noting that the GMPs require detailed written procedures and documented evidence for “everything you do,” he challenged the audience on whether their company’s standards, policies and procedures address the concerns Zachary raised – for example, whether their company has an event-capturing and management-notification program, and procedures and committees for fact finding, recalls and crisis management.

The Lachman exec urged the attendees to “go back into your event notification” to make sure that “any knowledge you have that your product is violative in the field” is getting “escalated up through the chain of command to the appropriate level.”

Zachary stressed the importance of having a system in place, in particular, to capture some of the “more atypical communications that are happening more and more frequently with FDASIA.”

She has noticed that company presidents are calling FDA directly when very serious issues or those with drug shortage implications arise.

“Companies have really good systems for tracking communication when that communication happens in normal channels through regulatory,” she noted. However, “the CEO is not so good at generating a regulatory activity report and making sure that it is fully documented in your systems,” and problems arise when discussions that are critically important “never end up memorialized.”

**International Consistency is a Challenge**

In her presentation, Zachary pointed to the need to be consistent in parallel communications with various health authorities. When situations arise that affect other agencies, “if you are communicating with other regulators and providing different or additional information that you are not sharing with FDA, that is going to make them uncomfortable as well,” she stressed.

Referencing the advice during the discussions, Janssen Regulatory Compliance Senior Director Eric Thostesen commented on the importance J&J places on having one consistent communication system. However, he pointed out, countries frequently ask for different or additional information that you are not sharing with FDA, that is going to make them uncomfortable as well,” she stressed.

Zachary noted that the issue comes up, for example, in relation to updating field alerts, and that her clients are now evaluating whether they have in place a communication plan for the various health authorities in this context. She advised erring on the side of oversharing – not assuming that the
inter-agency communication happens, such as between EU member states.

Sturgeon advocated building those types of decisions into standards and procedures.

Lachman had a client, he noted, that made IV solutions bags for the world market. “They had a contamination issue in Australia – the same line, same type of container made for the U.S. – but they didn’t notify FDA that they had a serious complaint for mold contamination. In your procedures, you need to have that decision tree built in there about how are you going to communicate with other global regulators and make that decision.”

Zachary added that “one thing that people often don’t realize about the field alert reporting is that if you have an issue for a product made outside the U.S. and distributed outside the U.S.,” and that facility is making a US-registered product with the same specifications, a FAR still needs to be filed with FDA.

ATTORNEY JENNIFER ZACHARY ON PRO-ACTIVE COMMUNICATION WITH FDA

This morning I thought I would cover FDA communications. That sounds like something that is fairly basic. But I spend about 50% of my billable time either reviewing communications that companies plan to submit to FDA or providing input on communication strategy…. So this is clearly something that companies could be doing more of in-house and getting more effective communications out of their company.

First we will cover the who, what, when, how, and why of communication, move on then to some common communication pitfalls, and then finally I want to discuss about six or seven different examples of actual FDA communication issues that I have seen in advising clients in private practice in the last three years.

And just as I did in my five-and-a-half years at FDA, I plan to be propped up by the expertise of others. So I have asked Roy, Karen, and Steve to share with us anecdotes and other experience from their time at FDA, as well as the extent to which they are able, from their time now in-house….

Criteria for Effective Communication

First of all, proactive, effective communication – what is it?

It needs to be first and foremost accurate. 18 U.S.C. 1001 is the criminal statute for misstatements to federal agencies and federal officers. This is not a place you want to find yourself. So you want to look at each and every communication that you make to the agency and make sure that you are accurate in the information that you provide.

You should also be informative. You don’t just want to dump a bunch of information on the agency and say, ‘here you go.’ You want to put it in a format that is actually something the agency can use and process.

You want to be timely. If you don’t communicate with the FDA soon enough, for instance, you miss your opportunity to build trust with the agency, and also to get feedback on your plans and take advantage of the agency’s expertise.

You want it to be actionable. You don’t just want to come to FDA and throw the cold dead fish on the table and say, ‘here it is.’ You want to say, ‘we have a problem, but we have a plan. What do you think of the plan?’ – as opposed to just leaving it to the agency to guide you.

You also want to be forthright. You can have a communication that is completely accurate, but it doesn’t contain all the information that would be useful to FDA. If it doesn’t have all the information that is useful, you may miss the opportunity to get feedback from the agency. You could also inadvertently mislead the agency by not including the full...
information that they would need.

You also need to think about the audience for your communication. Who is the audience? When you submit a communication to FDA there are a number of different constituencies. And this is one of those places that I feel like my clients often don’t appreciate that, ‘yes, you are absolutely communicating with technical experts, people who speak your language.’ So you are going to be speaking to GMP experts and people who are regulatory affairs professionals.

If you are making a communication that involves something about the drug – maybe you have particulate in a sterile injectable – you will also be speaking to the medical personnel in the review division, because those are the people who are going to look at your health hazard assessment and other documents and make an assessment about how this product’s quality issue could impact patients.

Then there are a couple other constituencies that, depending on the communication, may also be involved, [including] policy personnel within the center for instance, in CDER, the Office of Regulatory Policy (ORP).

You are also often, believe it or not, communicating with lawyers. Not only is the counsel’s office involved in a large number of things behind the scenes – like warning letters and reviews of FARS [field alert reports] – but there are lawyers sprinkled all throughout the FDA. Many people lament this, but this is the reality.

A lot of communications that I review for clients have a lot of assumptions built into them – for example, they talk about the LIMS system this and LIMS system that. Well, if you don’t put parenthetically ‘the laboratory tracking software,’ some of your constituencies are going to have no idea what you are talking about. So you want to make sure that you have the technical details in there, but you also have a little bit for the lay audiences within the agency.

In addition, you want to remember that your communications to FDA are going to form the basis of some other communications.

So if you submit a field alert, for instance, and you are a CMO [contract manufacturing organization], then you are likely under your contracts going to have to share that field alert with your contract customers. Also if you are in a co-development deal, where you make a drug with another company, you are probably going to need to share your field alert with them as well.

And finally, FDA can take your communication and make a press release out of it or some other public communication. Similarly, they could say, ‘you know what, we understand the issue but we would really like to see you do a “dear health care provider” letter. Can you take what you gave to us and turn it into that format?’ So you want to think about the different ways in which your communication could be used by the agency.

**When Proactive Communication is Expected**

FDA expects proactive communication by industry. It is really not optional at this point. I would offer a couple examples from the regulations.

The first is **field alerts and BPDRs** [Biological Product Deviation Reports], and especially field alerts. In three business days you do not have full information. It absolutely demands proactive communication of, ‘we have a problem, we are still getting our arms around it, but here is what we have.’

Another area where you have to communicate proactively with FDA is **recalls**. You know the regulations, although not mandatory, are recommendations given FDA’s lack of mandatory recall authority for drugs. They say you have to notify FDA immediately and then submit your recall strategies so you can get feedback from the agency. You are not supposed to delay in implementing that. The sooner you reach out to FDA, the sooner you can get feedback and be confident in your strategy going forward.

And the same is true if you are going to send a communication out to your **customers** in the context of a recall. FDA is going to want to see that. They are going to want to have you send that out promptly to the customers and other
people who may have the product.

Congress also expects industry to be communicating proactively, the most recent example of which are several new provisions in FDASIA, the FDA Safety and Innovation Act. In it—and I think this is a huge game changer, and it is one that we haven’t really seen come into effect yet because FDA just promulgated the regulations in draft in November—is drug shortage reporting. And under this, there are going to be all kinds of preliminary proactive communications with the agency because it is now required by law.

So if you have an issue, a GMP issue, or some other issue that is going to be reasonably likely to affect your ability to meet your orders and produce product, you have to communicate that to FDA. Now the standards are a little mushy. The regulations are still in draft. I think the details are going to get worked out, but that is absolutely going to require companies to come forward and share information about problems that likely would not have come to FDA’s attention until the market started to experience problems.

Another issue is FDA’s authority now to request records in advance or in lieu of inspection. So far I have not seen FDA use this authority as frequently as I would have expected. Mostly they are using it [in situations where] they came out and did an inspection, and they probably should have picked up a few other records, and they are using it to kind of ask for the records after the inspection. But this is another area in which you send a field alert to FDA that is telling a pretty narrow slice of the story, and they can just send you a request for all the related documents, the investigations, and everything. So I think these two authorities are really going to be interesting as we see FDA implement them.

**Why Communicate Proactively?**

So why would we want to communicate with the FDA proactively? This assumes that you are in a situation where it is not mandated—like a field alert—a situation where you have an issue and you want to go to the agency and talk about it.

I think the first reason and the most powerful one is it gives you, the company, the opportunity to frame the discussion for the agency. And perhaps even to forestall inspectional observation.

So if you say to FDA, ‘whoa, we found this thing. It is a problem. But here is how we are addressing it and here is our plan.’ If they come out and inspect they are going to appreciate that you let them know that there was an issue. They are going to appreciate that your quality system was working and you uncovered this issue. And sometimes investigators will give you credit for the work that you have done, with the assumption that your plan was not to get to steps D, E and F until a certain date. And in those instances sometimes they will hold off on citing it in a 483.

**Mahoney:** Can I chime in? I have a few thoughts on this. Jennifer and I worked together at FDA and I also work with [Karen Hirschfield] in CDER Compliance. So this is a topic that's near and dear to many of our hearts.

‘Why communicate’ sounds like a basic question. I have had many companies ask that when I was practicing law and the first response is generally, ‘why not?’ There is obviously a way to do it and way not to do it. But there are times that it’s appropriate. And in those times probably the number one thing you need to show is the appropriate tone. As you have probably all seen many times, the tone is defensive, the tone is argumentative. I can tell you first hand that is not the right approach. It is actually probably the worst approach you can take. That is why it is helpful to have outside counsel or multiple levels of review to make sure the tone is appropriate.

In terms of advising companies or even at FDA, working with [FDA Regulatory Compliance Director] Joe McGuiness and others at the district, the big ticket is you want to show FDA that the company gets it. The big ticket, ‘we get it, we understand what is going on.’

In terms of the relationship, I always say FDA and pharma is a long-term relationship, so you need to be careful with
how you manage that. Part of that is effective communications, showing that, ‘yes, we get it. We understand there is a problem. We are taking these steps to correct it. Those steps will be completed by a certain date and these are the measurable actions.’ So, again, kind of high level, make sure the tone is appropriate – make sure the correspondence shows, ‘we get it and we are making progress.”

**Zachary:** Thanks Steve. I think another reason to communicate proactively is to dispel confusion about the situation.

I am often asked to review field alerts. I will read them. You know, those little boxes don’t exactly give you a lot of room to elaborate. Some companies elect not to attach narratives or other things to the field alert. I will read the field alert and I will really have no idea what happened or what is going on or what the plan is to address it. So I will say to the company, ‘help me out here, explain.’ They will provide the investigation and all of the supporting documentation, and suddenly I get it. But how it is that they think someone at FDA is going to pick that up and understand the story without those supporting documents isn’t clear to me.

An important thing is to build into the communication the information that FDA needs. Don’t bury them in documents. Don’t necessarily always submit the investigation, but give them enough substance that they can sort of begin to understand and dispel some of their confusion.

Another reason to communicate proactively is to build trust and a good relationship with the agency. If your district office knows that if there is a problem and they are going to hear about it, they are going to be much less skeptical when they deal with you. They are going to want to work with you. They know that you are good actors and if you had a problem it is not for lack of vigilance or that sort of thing. It is all part of your relationship building – being transparent with the agency.

Another reason why – and this is especially important with the new FDASIA drug shortage reporting obligations – is that when you report issues to FDA you can get assistance from the agency. Not just technical expertise and other things, but also they have a number of tools in their tool kit to help companies that encounter problems.

Let’s say you discover you have a problem with a piece of equipment, and it is a really important piece of equipment. It is actually going to be a prior approval supplement [PAS]. That could delay manufacturing for a long period of time. But if you have come to FDA, explained the situation, explained that ‘we need to swap this out,’ they have tools at their disposal to accelerate that. I had a PAS go through in a week-and-a-half – that is not typical FDA processing time, let’s be honest. So reaching out to the agency can actually take advantage of the numerous tools that they have available to them.

Another issue is to get feedback on your corrective action plan. You don’t want to go to FDA with a half-baked plan. But if you have a good plan and you outline what you want to do, it can be very helpful. They are never going to bless it and say, ‘oh yes, if you do that, that would be perfect.’ But they may say, ‘have you considered x, y, or z,’ or ‘at the end of the day we are going to want to know the following things.’ You can build that into your plan going forward. It is a lot easier than at the very end having to go back and try to figure out that ‘FDA also wanted to know this, and we didn’t look into it the first time around.’

Also – and this one is critically important – if you plan to make public communications about the situation, FDA very much wants to be involved in helping you frame the message. Remember, they are here to protect the public health, and the ‘public’ part they take very seriously. If you send out a communication that FDA hasn’t had a chance to view and help you provide clarity or context, they could be very unhappy. Of course the agency has its disposal a very loud megaphone from which they can issue their own press releases and other corrective communications. You do not want to be in that situation.

**How to Target for FDA Needs**

How do you communicate most effectively? I think that the first thing that you want to do is think about, ‘if I were FDA and this particular area was my responsibility, what would be my concerns? What questions would I have?
What information would I want to know? What would I want the company to be doing?’ So think about it from their perspective.

Then remember that FDA has very limited resources for the tremendous swath of industry that it has to supervise and monitor. So if you just provide them all kinds of data, all kinds of reports, they are not going to be able to work through that information and give you actionable advice. So give them something they can work with – give them the bullet points and offer to provide the supporting materials if they want them. I think that is a better strategy than sort of dumping it on FDA and letting them sort it out.

Another thing that is really important is removing internal references. We all speak the language of our companies and we don’t realize that that language doesn’t always translate outside of the companies. You want to make sure you are not abbreviating things when FDA won’t know what they mean necessarily.

You also want to remove or at least define the technical drug name for lay audiences so that people understand what you are talking about.

Again, you should – and this is just a shameless plug – consider legal review. One reason why you should do that is that lawyers, even if they are not technical experts and many of them are, but even if they are not, they are trained in analytical thinking and they are just generally going to lead your document and ask the kinds of questions that those audiences within FDA that I mentioned are also going to ask. What is the press office going to have a question about? What is ORP going to have a question about? So they can make sure you are addressing all of your target audiences.

Another thing that sometimes trips companies up is communicating different information in different ways to either the District or the Center within FDA. So you give partial information to the district. Then when you start talking to CDER they ask you different questions and you give them more information and the District is like, ‘hey, if we had known that, we would come out differently, too.’ There is no faster way to sort of upset your district then to provide them with limited information and then it goes up to the Center and the story changes. So you want to make sure that you communicate consistently and that you are checking back in to make sure that all the information was provided to all of the relevant FDA parties.

Sometimes people think, ‘well, I sent that to the review division, so it must be at compliance’s fingertips,’ or, ‘of course the investigator in the district got that, it went to the review division.’ That is really not how it works within the agency. There are systems where they could get that, but it is just not the typical way that you would go about getting information. So it's better to over-distribute than to under-distribute.

If you have a situation that is going to affect the EMA or other agencies, if you are communicating with other regulators and providing different or additional information that you are not sharing with FDA, that is going to make them uncomfortable as well.

Sturgeon: Can I chime in? I appreciate the shameless plug. The second point is so painfully obvious, but I think it is so important to see in terms of the right amount of information. That is the million dollar question or million dollar discussion that needs to be had.

When I was at FDA or advising companies, I would say, ‘the kitchen sink approach is not a good approach.’ FDA doesn’t have the time to sift through all the homework that you did in the day by day, month by month process for progress you are making. You really do need to be clear and concise and present the right information to the right audience, understanding if it is the district, or compliance, or the review staff. And so taking time upfront to kind of have that discussion can save a lot of time.

The kitchen sink approach is a great way to raise a lot of questions, some of which really shouldn’t be asked, or really aren’t questions but just cause confusion. And that is the kind of confusion that you don’t want to have, with FDA at your door asking fifty questions that really either could easily be answered or more questions that were basically raised because of the confusion in your document.
What to Communicate and When

Zachary: Sort of piggybacking off that last comment, what should we communicate?

You can be communicating with FDA about a discrete issue – for example, regarding a packaging line where you think there is a possibility that three lots had incomplete lot numbers.

But you can also go to FDA proactively and communicate about much bigger broader issues. If you discover a significant problem that is going to take quite a while to fix – maybe it requires hiring additional resources, putting in place new equipment, but you have a plan for all that – you can go to FDA and say, ‘look, here is the situation. Here is our plan going forward that we wanted you to be aware of. We wanted to communicate proactively.’ Like I said, there could be benefits to that in terms of having self-disclosed issues to FDA. Keep that in mind.

In addition, when you communicate with FDA, whatever you submit you want to give the agency enough information to know that you are handling it appropriately. You want them to feel like they don’t have to get involved – that you are looking at the right things, addressing the right questions, and that you adequately evaluated product impact early on, as well as if a health hazard evaluation is needed; that there is no patient safety concern. That is going to be FDA’s very first question when you communicate with them, so you want to make sure you are answering those questions.

In a lot of situations, especially with field alerts, you are not going to have much information at all, but you have to communicate anyway. In those contexts it is really helpful to tell FDA, ‘we don’t have answers, but here are the questions we are trying to answer – our investigation is targeted at answering those,’ so that FDA has the comfort of knowing, ‘ok, they are on the right path.’ In addition, you want to tell them, ‘here are the next five things we are going to do. You are going to hear back from us in ten business days with an update.’ That way FDA doesn’t have to be nervous that they have been alerted to this issue and then you go radio silent. Finally, you commit to providing them with regular updates until you have resolved the issue.

Obviously, you should communicate proactively. That said, you can communicate too early. You don’t want to reach out to the agency when you really don’t have sufficient information to even let FDA know what to do with it.

There are situations where you may want to reach out with very limited information, but those would only be in situations where potentially it is a very serious public health issue. Otherwise, it is a balancing act. You want to get to the point where you have enough information to tell a story to FDA that is informative and useful information, but not so far along that you can’t change course if the agency has different ideas.

So in trying to decide when to communicate with FDA, I would suggest that you think about, one, the seriousness of the situation for the public health. Think about the likely product impact. And think about the length of time that you would need to really conduct a thorough investigation. If it is only a matter of a week or two and it is not a particularly serious public health threat, it might make sense to fully investigate and then decide whether or not you want to communicate with FDA or if it is just something you can document in your records.

Hirschfield: I am not a lawyer, but I still do need to make a disclaimer that my views are really from my days at FDA in many ways – particularly when I was the acting branch chief for CDER recalls.

I just want to chime in on when to communicate, because there were very good examples of good companies who would let us know within the agency when a situation was happening, in progress, and there was the potential for serious public health impact or perhaps even drug shortage. And in those instances, if those companies contacted us early we were able to get the subject matter experts within the districts and the review divisions, if needed, on board very quickly and we could resolve issues very quickly. But that is when the agency was given enough time to put some things into place.

In contrast, some of the companies would wait a little too long. And it is obviously very hard to know when the right time is to contact the agency. But when they would wait too late and the FDA’s back was up against the wall, it really created a lot of problems – both for the agency and for the company – because in many ways it was too late to do anything proactively.
So perhaps if there was a shortage involved we could try to import products from outside the country to alleviate those drug shortages. But if it was already at a critical stage, we couldn’t do that. At the end of the day the public was who suffered when the patients didn’t get their medicines. And that is what we were ultimately trying to prevent.

The other thing I would like to mention is about when and who to contact. For GMP issues, really the district offices are the first place to contact. Going to the Center first just is not a good idea. It does create some conflict. There are certain situations like preapproval inspections and perhaps CMC issues where you do have to make those contacts.

In a general sense, for GMP issues you should make the district offices your first point of contact. By doing that, it sets the big wheels of FDA in motion and all the appropriate places will be contacted. The districts offices are great at doing that. They have those mechanisms in place and have had for a very long time.

**Sturgeon:** One point on a high level I have always thought – when you are calling FDA with a question, some things that should always be in the back of your head: Before you have that call, ask yourself or have the company ask themselves, ‘are we asking FDA to be a regulator here or are we asking FDA to be the expert consultant?’ I know in a later slide you mention that, but it is always worth considering.

If you are just kind of calling up looking for advice, there are other people to do that. There are consultants. There are law firms. There is a lot of expertise in the industry. Before you pick up the phone to have your friendly phone call with the district – which is incredibly busy with inspections or with other work plans – ask yourself that question. It is always a worthwhile exercise.

**Zachary:** So if there is an issue that you should have communicated to FDA but you didn’t, and FDA is now out on an inspection and they find it themselves, you are going to lose credit for not having been proactive and transparent with the agency. But once they discover the issue, if you are open and forthright and provide them with information and not make them draw you out with each question, you still get credit, and you can still build trust with the agency and take advantage of the expertise of the investigators that are there on site with you.

### Common Mistakes

One of the common mistakes in communicating with the FDA that I have seen in my time at the agency and now in advising clients in private practice is **waiting too long.**

We all have this instinct that FDA is going to overreact or they are going to start importing product from one of our competitors – that they are going to take some dramatic step, so we should just wait so we can have a little more data and a little more information so they understand that this isn’t such a big deal. I think that doing that can often be a mistake. As challenging as it can be to go to FDA with an incomplete story, I think that if you explain to them what the next steps are you have a pretty good chance of having them see it your way as well.

Another one, and we have talked about this already, is that people have a tendency that if they are going to share they want to **give FDA everything** and they don’t really organize their submission. They expect that FDA just has teams of people sitting around with all this extra time to read deviation reports and do other things. That is simply not the case. You want to give FDA some limited information at the beginning and tell them the other things that are available if they want them. Let them kind of reach out to you and guide it from that point.

Also there is a temptation – especially in your initial FARS, where you have so little information – to assure the agency that everything is ok. And so you make **broad, conclusive statements** about there being no quality product impact. Remember 18-USC-1001, false statements to federal authorities – you don’t want to find yourself there. It is perfectly fine to say that ‘all evidence to date suggests… ’ Indicate that you are still investigating and that there are still issues you are running down, and that you will find answers and you will report back on those answers.

Also as Roy said, don’t treat FDA like your **expert consultant.** There are experts for that reason. You want to go to FDA with a plan of action and basically ask them for feedback on it. Don’t expect FDA to bless your plans. Don’t expect FDA not to have different views when someone else at FDA looks at what you have done. You really want to make sure that what you are doing is the appropriate course of action.
Even if you have a discussion with FDA, that product is your product. You are the one with the allegedly adulterated product or allegedly misbranded product. You are responsible for that product at the end of the day even if you have run your plans by FDA.

Sometimes clients ask questions that they really don’t want answered. If you have a plan of action and you want to do X, if you ask that question to the FDA and they say ‘no,’ that is a no. That is a hard no. If it is something that is legally permissible and you have a good strategy and you want to go down that path and you feel comfortable, then you should just do it. Don’t ask the question where if the FDA says ‘no,’ then you are suddenly stuck.

Case Studies

Now I would like to talk about a number of case studies that have come to me both when I was at FDA and in private practice.

CASE STUDY 1

The first one is a situation where a company sent a field alert to FDA alerting it to the fact that it had discovered some pretty serious contamination in its API. They went ahead and made a large amount of final product by the time they had discovered the problem. There is also a lot of product on the market.

They had determined internally after consulting with a lot of medical experts and others – and I think this was a pretty sound rationale – that a recall of this particular medication, because of the patient population and some other things, could very likely result in patients stopping their treatment for a period of time over concern about this recall and contamination. They decided not to do a recall and to simply remove the stock that was at their distributors and replace it with other products.

They submitted a FAR to FDA that basically had this plan laid out. It could have been more detailed and better explained, but they did submit a FAR. They did not hear anything.

Six months later, FDA came out to inspect. They looked at the deviation report related to this API, and then lo and behold, they found the field alert. Clearly someone in the district had read it, but it hadn’t made its way to these investigators. They were not at all happy with this decision not to recall from top to bottom. They were pressing the company very hard for the recall.

The company got an observation related to this.

In their 483 response as the corrective action the firm said, ‘from now on every single time we send a field alert we are going to call the district and follow up and say, ‘hey, are you guys ok with this?’ So FDA’s response was, ‘oh no, no, no, we do not want to hear from you every time there is a mixed tablet report from a customer or from the pharmacy. That is a waste of our time. We want to hear from you, but we want to hear from you for things like why there is contamination in your API.’ FDA wasn’t very happy with their revised SOP.

The lesson here is to communicate with FDA only when it is going to be useful to the agency and useful to the company. Sort of using emails or calls to FDA as a CYA is not a good policy. It is not something your district is going to appreciate. And ultimately it is not going to protect you at the end of the day, because when FDA does get around to looking at what you have done, you remain responsible.

CASE STUDY 2

Another case study is about a company that submitted a field alert to FDA because it had distributed product that was made with a manufacturing change that was the subject of a CBE-30 supplement. The company had implemented the change and distributed product before the thirty days had run. They now had product on the market that hadn’t technically complied with the specifications in its application.

So they submitted a field alert to FDA with both an initial and a final saying, ‘look, there are these three batches out there. We are not going to take any action with them.’

A little problem – in the field alert they admitted the fact that months before they had submitted the CBE-30 they had
actually distributed product made with that change. They filed the CBE-30 because they realized they had made a change that should have been filed in the first place. Initial drafts of this field alert contained this information, and at some point in the review process the information about the previously distributed batches was removed.

This is a very tricky thing – hard that it would ever get caught. But you know how it does get caught? The Department of Justice has different requisite authorities than FDA. They can issue a subpoena for basically every electronic document you have. They can look at versions and version control, and that is exactly what they did here. They saw that the company had additional information that was clearly material to FDA. They removed it, and DOJ was not happy.

The case has not been resolved yet but it is one of the issues DOJ has identified to us as supporting the criminal case they are bringing against the company as well as individuals. This is scary stuff. You don’t want to communicate incomplete information.

You are going to make mistakes, like making a manufacturing change that you should have filed to your application. It is better to disclose that to the agency than to have someone, FDA or DOJ, find it on the back end. The consequences can be severe and it can result in you going to prison.

**Mahoney:** I just have something to say to this last point. It seems obvious that mistakes happen. As we all know, mistakes will happen, and FDA can probably say it expects them to happen. This is an industry that is moving quickly and there is a lot of activity.

It is not the fact that mistakes will happen, but FDA is obviously concerned with what you are going to do with them, currently and in the future, and then take it back a step back and look at kind of a global systemic perspective. In reality, not having problems, not having mistakes, is probably more of a red flag than having mistakes.

**CASE STUDY 3**

**Zachary:** In another case study, a product had a minor issue that did not affect product quality. The drug is absolutely safe and effective. The company consulted with its local district and got what it believed was agreement about its path forward for a market withdrawal, in light of the fact that the company did not consider it to be truly violative.

But then the situation became controversial and well publicized, and suddenly the agency, once it got to the highest levels, had a different view than the individuals who were consulted in the district. And when that happened, this lesson came home. And it is a very hard lesson.

I think can be unfair to a lot of companies: Individuals within the FDA are happy to offer their expertise and their input. But if they are sending you emails or having discussions with you that are not formal, they do not represent the official position of the agency. Ultimately, the company remains responsible for the products that it distributes. And if something becomes controversial, or the agency gets pressure from Congress or others, it may very well take a different stance than it did.

In the example that I was describing before about regulatory discretion, FDA now has a way where it will issue letters to companies that say, ‘we are exercising regulatory discretion for your misbranded product for the following reasons….’ That is a document that is not the informal statement of an individual within FDA. That is coming out on the agency’s letterhead. It is saying to the company that FDA is going to hold off on enforcing the Food, Drug & Cosmetic Act with respect to this one discrete issue.

But even those letters at the bottom say that you remain responsible for complying with the Act and the agency wants to hear from you if there are any safety signals with respect to this product and all of those things.

**CASE STUDY 4**

This is an example of a positive communication. This is not a miscommunication.

One of my clients had a product with only a 12-month expiry, and it was a product that was in desperate shortage.
It was needed by the market immediately. They had an investigation open that had prevented the release of most of a lot. They are finally about to close the investigation and they realize that this product has, depending on the lots, anywhere from one to three months within expiry remaining. Given the need for it in the market, they felt confident that if they got it out the door that pharmacies and hospitals were going to use the product even if the date had passed. It was a drug that people desperately needed.

There was some debate internally, about, ‘hey, if it is within expiry when we ship it, it is not our problem.’ Other people within the company prevailed. They went to the agency and they said, ‘we have this product, we know that the market needs it. Here is some limited data that would support a slight extension of the shelf life. What do you think?’

FDA, just like Karen described, got a team together, moved very quickly, and actually permitted the company to distribute those specific lots. They included a ‘dear health care provider letter’ and really facilitated the distribution and assuring pharmacies and hospitals, saying, ‘oh yeah, it’s good, go for it.’ That kind of cooperation with FDA is only possible if you reach out to them. The company was able to have a lot less anxiety about what it was doing because it knew it had this official position of the FDA backing them up on this decision.

So when you communicate with FDA – and this is going to become all the more crucial with the drug shortage reporting under FDASIA – you really want to explain to them, ‘here is the public health impact. Here is why we need some assistance from you. Here is why we are doing what we are doing.’ Give the agency a plan: Say ‘we need four months of extension’ – or ‘we need to be able to distribute this product that is unapproved in the U.S. for this limited period of time until our second supplier comes online.’ Give them an action plan that they can bring a team together to evaluate, maybe tweak, and then sign off on.

CASE STUDY 5

Another case study is about communicating with the public. One of my clients decided and felt very strongly that they had a Class 3 recall on their hands – not a big issue at all. (I still believe that FDA has never seen a Class 3 recall. It is Class 1 or Class 2.) They went ahead and communicated broadly with their customers, because you don’t have to wait for FDA to sign off on your plan. This went pretty far down, not just to the first wholesaler.

FDA, when they got around to reviewing the plan, disagreed with both the classification and depth. They required the company to reissue the communication, which created all kinds of confusion. FDA also broadened the number of lots that were impacted. And so the company got back basically everything they had made when it really was only a window [that contained the problem], but people were confused and frustrated and sent it back.

CASE STUDY 6

Another situation is a client who had particulate in its vials. They did not have a persuasive public health message they could take to FDA about drug shortage because, although they didn’t have sufficient inventory that wasn’t impacted, there were other companies that made products that were similar that could address the health condition.

The company realized they were not likely to get very far if they approached drug shortage about some sort of regulatory discretion. So they took it upon themselves to send out a ‘dear health care provider letter’ that said: ‘You have our vials. Pick them up and take a look to see if there are particulates before you use them.’ That did not go over well. FDA was really unhappy and they ordered a recall, not surprisingly.

FDA is very watchful and concerned when companies are communicating with the public about potential safety and effectiveness issues, and they want to have an opportunity to view the communications and provide input and make sure that they are readable by the audience they are going to and all those other things. So if they don’t like the way you have communicated, they will use their press release authority to correct your communication.

CASE STUDY 7

Alright, the last case study. This one is the one I have had maybe the most difficulty in convincing the particular client was a good idea. So far, in the first four or five months, I think it is working out quite well.
The company had pre-inspections of increasing seriousness. At the last one, the investigators were basically saying, ‘we are just so terribly frustrated with you.’ The company makes medically necessary products for very important indications. And their last one is a blockbuster therapy that got up to the agency, and the review division approved it over the strong objections of CDER compliance, which felt like the manufacturing facility was so out of compliance that they couldn't sign off.

But when the review division did this, they did so with a number of conditions upon the approval, which is something I have never seen before. It almost looked like a mini-consent decree. It involved a third party coming in to look at data and processes for each batch that was going to hit the market.

The company realized, after they brought in a third party to look at their situation, that they had some really serious fundamental problems. And that is why FDA was coming up with the observations. But these weren't the kind of problems you could fix before your next pre-approval inspection. They have a pipeline that is very impressive, but they were worried about the idea that ‘if we go to FDA and say we have these problems they are not going to approve anything in the pipeline for the 18-24 months it takes us to fix them.’

Ultimately realizing that they were running out of time and these inspections were getting worse and worse, they put together a plan with step one and a date, step two and a date – essentially like the remediation plan that Roy was describing for a consent decree. They took it to the district, and along with it, did kind of a ‘coming clean.’

‘You haven’t seen it yet, but whoa, when you see our complaint backlog….’ They sort of laid it out there and said, ‘this is why it is going to take eighteen months for these fixes. Here are the positions were going to hire. Here are the people we are going to bring in.’

FDA did the last pre-approval inspection and they inspected against the benchmarks in the plan. They didn’t ding them for not having gotten to the end of the plan. I think it has been really effective. I told the agency that the company gets it and that they are going to fix it and that you can trust us. So far, I think it is really helping the relationship with the district. It is making it a lot easier for the review division and for CDER compliance to be communicating about their applications.

I think that communicating proactively and effectively can really help you manage your FDA relationship. It can also give you some breathing room and some space to make lasting corrections when these aren’t the kinds of things that can be addressed in your 15 business days following your inspection.

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Success of Eight-Year Amgen Effort to Improve Deviation Investigations and Follow-up Actions Writ Large on Quality Metrics and Bottom Line

The results of an eight-year program at Amgen to improve its deviation investigations and follow-up actions demonstrate how concentrating on finding and addressing root causes can have a substantial impact on a firm’s quality assurance and bottom-line.

Amgen’s learnings on its continuous improvement journey have strong relevance to the current discussions on manufacturing metrics – shedding light on which can more clearly reflect the process improvements that matter to product quality.

At an ISPE conference on “pro-active compliance” in New Brunswick, New Jersey in January, Amgen Quality Science Senior Specialist Jill Peirick provided a revealing look at the progression of her company’s deviation investigation program and how the changes Amgen has made are reflected in highly significant declines in the number of errors per lot, distribution cycle times, and scrap.

Amgen’s focus, she stressed, has been on reducing errors rather than the number of non-conformances, adding that the latter metric is subject to manipulation in ways that could be counterproductive to product quality assurance.

Amgen’s Journey Provides Roadmap

Peirick began with a depiction of where Amgen was in 2006 when its “continuous improvement journey” was getting underway, and provided an engaging color commentary on how her firm has refined its deviation program since then to improve its QA capabilities. [Editor’s Note: Peirick’s complete remarks are provided below.]

Her description of the Amgen process provides a valuable roadmap for other companies that are striving to progress down a similar pathway.

In 2006, nonconformance (NC) investigations, in general, were equally staffed, independent of the risk that the deviation may have posed. In addition, the firm had a backlog of incomplete investigations, which “meant that we were not making it a priority to address the issues,” Peirick commented.

An important first step was to classify deviations based on risk and assign more resources to those with greater potential impact. This was followed by improved trending of non-conformances to help in the risk-ranking process.

The improved management review process put in place in 2008 is another key step.

The reviews do not focus only on NC metrics, but tackle “the tough things,” and tend to be “noisy” and “difficult,” Peirick stressed. She likened some of the meetings to running a marathon, with a great feeling of accomplishment at the end.

The meeting participants also set a tone within the broader organization that encourages employees to come forward with issues and “push them up the ladder so that everyone knows what is going on and can be on top of it.”

Key Ingredients in Improving Investigation Program

In her presentation at the ISPE conference, Peirick explained how Amgen’s success in its investigation improvement program flowed from its emphasis on:

- science-based decisions
- standardizing investigations
- implementing investigator training and certification programs
- creating an independent internal department to focus on and oversee critical investigations
- understanding the difference between causal factors and root causes, and
- the involvement of senior management using a defined process to gauge the quality of deviation investigations and the resulting action plans.

Following the revamping of the management review process, the development of a standardized methodology for conducting and reporting root cause analyses and of a technical report writing course served to improve the quality of the deviation investigations and streamline their review process.

Investigations Overseen by “Quality Sciences Team”

The next “big” step in improving the quality of deviation investigations was the creation in 2011 of a “Quality Sciences” team – an independent, cross-functional group of experts that helps oversee and guide the process.
Peirick – a member of the Quality Sciences team – commented that the independent nature of the team allows it to “ask the tough questions, force the tough issues, and really force people to think outside of the box.”

The team’s primary responsibility is to ensure that Class 3 investigations – those with the most potential for product quality impact – are properly scoped and conducted.

Within seven days of a Class 3 NC being opened, the investigator is required to submit to the team all the information and investigations taken at that point.

The Quality Sciences team makes sure the investigation is on the right track and has considered whether other product lots may be impacted. As the investigation proceeds, the team convenes an “advisory board” that includes site quality heads to further evaluate the Class 3 investigations and provide additional guidance.

### From Whipping Boy to Golden Child

In spite of the tools and processes Amgen created help standardize and streamline the non-conformance investigation and review processes, the job of the investigator remains a difficult one.

Peirick commented that NC owners “get push back from everybody” – including those wanting to release the batch in question, close out the investigation to meet timeline metrics, and put equipment back in service.

To ensure that the right people with the right skill sets are leading NC investigations, Amgen developed a qualification program for Class 2 deviation investigators and a formal certification program for those leading the Class 3s.

The certification program includes mentoring by experienced senior management and formal evaluations of investigations that must meet strict criteria for an investigator to become certified.

An important part of the training and certification program is the course developed internally on technical writing that, in addition to teaching scientific writing skills, teaches the concepts of “claims, reasons and evidence,” and inductive versus deductive reasoning.

As trained investigators guided by the Quality Sciences group began to show positive bottom line financial impacts, the perception of those performing the investigations began to change.

At Amgen, Peirick commented, NC investigators are now “highly regarded, very well respected, treated very well, and they have become not the ‘whipping boy’ anymore – they are now kind of more the ‘golden child.’” The investigators feel “stronger” and “more empowered” to expand the scope of investigations and to ask tough questions.

### Improving Investigations Requires Lifestyle Change

Inadequate investigations have perennially been high on the list of regulatory agency inspection findings – independent of the agency conducting the inspection – and one of Amgen’s goals is to “get off the list” of firms that receive that citation.

Peirick emphasized that it will take “effort and commitment” to reach that goal and that it “is not going to happen overnight.” She characterized the effort needed as a “lifestyle change” – more like enrolling in a weight loss program as opposed to going on a diet.

Peirick was asked how Amgen freed up peoples’ time to perform investigations “during a time of headcount reduction and increasing workloads.”

She explained that as her team was working with quality units and quality functions, it was also looking outside at other groups and “whether what they are contributing is necessary and value-added” and how resources could be shifted to higher-value activities.

“What we have done at Amgen is dedicate FTEs specifically to being NC owners,” she stressed. “That is their job. That is what they do. They own Class 3 NCs. They are at every site.”

Regarding higher-level resource allocation across the company, “that is done by the guys upstairs,” she said. “We just continue to push forward every day to do our jobs and give them the data to show why it is of value to them.”

When the questioner commented that dedicating full-time

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### Amgen’s Continuous Improvement Journey

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<tr>
<th>Year</th>
<th>Improvement</th>
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<tr>
<td>2006</td>
<td>Instituted Risk-Based Classification System and Class 1 Nonconformance Quick Close Process</td>
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<td>2007</td>
<td>Improved Trending of Nonconformances</td>
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<td>2008</td>
<td>Improved Management Review</td>
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<td>2010</td>
<td>Standardized Root Cause Analysis</td>
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<tr>
<td>2011</td>
<td>Developed Technical Writing Course for Investigators and Involved Quality Sciences in Investigations</td>
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<tr>
<td>2012</td>
<td>Initiated Investigator Mentoring, Qualification &amp; Certification Program</td>
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resources to investigations is expensive, Peirick concurred, noting that the Quality Sciences team “is not cheap.” She added that the travel budget is large “because we are sent where we need to go,” but that “it pays back ten-fold. It is a great investment.”

**Target Evolves to Measuring CAPA Effectiveness**

Closely related to the adequacy of investigations is whether preventive actions put in place actually solved the problem.

The Amgen Quality Sciences team member commented during the Q&A that initial efforts in the deviation investigations program focused on the non-conformances, followed by a refining of the CAPA process. CAPA effectiveness verification (EV), she said, “is the next area we are improving.”

The team is “struggling with setting the right criteria to define success – to define an effective CAPA.” For example, if the measure of success is no recurrence of the problem for a year, that would not be sufficient for a process that is only run twice each year.

Peirick’s team is working with NC owners on how to set “realistic” acceptance criteria and to understand what would “truly demonstrate that something is effective.” She pointed out that TrackWise software does have a provision for recording a CAPA EV record.

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**AMGEN’S JILL PEIRICK ON IMPROVING THE DEVIATION INVESTIGATION PROCESS**

At the ISPE Pro-Active Compliance Conference, Amgen Quality Sciences Senior Specialist Jill Peirick provided a revealing look at how systematically improving her company’s deviation investigations and follow-up actions advanced Amgen on its continuous improvement journey.

I came here from Colorado on Sunday. On the way to the airport, my 5-year-old asked me why I was going to New Jersey for work. I told him that I was going to talk to some people about conducting investigations. He asked me, ‘what is an investigation?’ I told him, ‘well, you know when you have a problem and you have to solve it, and you have to figure out why it happened in the first place, and then you have to figure out what you have to do to fix it.’ He just sat there, and then you could see the light bulb click on, and then he said, ‘just like Scooby Doo and Shaggy’ – solving a mystery.

So what I am going to talk to you about today is Amgen’s journey of going from probably what looked a little more like Scooby to what we have today, which looks a lot more like Agatha [Christie], in our attempt to improve the quality of our investigations.

The first thing I am going to do though, since I realize that I am standing between you and lunch – I will give you an out. I am going to tell you the three key points of this entire discussion, so feel free to get in line first.

The first thing is, in order to build a sustainable program – everyone has been talking about sustainability – to understand it is not going to happen overnight. There is no quick fix. You don’t get the fancy acronym for your new project. You don’t get a t-shirt that advertises it. It is not the buzzword of the week.

The second thing you need to realize, from an investigation standpoint, is that distinguishing between causal factors and root causes is critical. If you don’t understand the differences between those two things you will never get the right corrective actions. You will never prevent the issue from happening again.

The third piece is that investigations are critical to your business. They are critical to the quality of your products, and therefore the health of your patients. And you don’t have a business if you don’t have healthy patients. What that means from a maintenance perspective is that you must remain diligent and you must make it a priority. It is not ‘throw money at it, get the t-shirt, and walk away.’ It is ‘continue to fund and continue to push and continue to improve….’

**Science-Based Decisions**

When it comes to investigations, using science to drive the decisions you make makes sense. We use science all the time. But I think sometimes we get lost in, ‘are we really applying scientific method? Are we really answering the right questions? Or are we trying to find that easy fruit that is right there to pick because it is less painful?’ So we have to be...
applying scientific rigor to investigations that require it. We obviously have to be documenting it well, because when that FDA auditor walks in the door they know nothing that you know from the investigation perspective. All they know is what you tell them and what is written down on paper.

From Amgen's perspective, we did not want to just reduce the number of non-conformances [NCs], because you can do that in quite a few ways, right? You can all manipulate your metrics. You can say, ‘well, this one I am going to decide really isn’t a non-conformance. There – I just dropped my number of non-conformances this week.’ Or you could say, ‘you know we have these two issues. I will bucket them both in one NC record, and then we have just decreased them by 50%.’ You can’t do that when you are trying to reduce errors, and that is what we were attempting to do – not just reduce the number of non-conformances.

One thing I know from being in industry for quite some time is that we have always talked about investigations, and improving the quality of investigations as being good for compliance, which it is. But I am going to argue to you today and demonstrate to you that it is also good for business. Someone yesterday asked, ‘how do I convince my management to continue to fund these programs that are successful? Because they think once they are implemented, we are good to go.’ I will show you and demonstrate to you the information you need to convince them that it is critical to their business, that it will make them money, and they should therefore support you.

We all know this, this is nothing new: Inadequate investigations are always high on the list of issues identified during inspections. It doesn’t matter what agency you are talking to. It doesn’t matter what year you are talking about. It almost doesn’t matter which company. Failure to investigate adequately – we see it all the time.

So I am not telling you anything you haven’t heard before. But what I am going to tell you is that it is going to take effort and commitment to get your name off of the list. It is not going to happen overnight. It is a journey. It was [J&J Quality VP Veronica Cruz] yesterday who talked about losing weight by getting on a weight loss program. This isn’t just a diet – this is a lifestyle change. And you have to be diligent. You have to watch out for drift. And you have to make sure you are on top of it.

Continuous Improvement Journey

As I mentioned, Amgen has been on a continuous improvement journey.... It started back in 2006. I would say we were feeling kind of unhealthy when it came to our non-conformance program. We didn’t necessarily assign resources in the most critical places where they were needed. It was more kind of across the board. This NC gets an investigator, this NC gets an investigator, even though one may have had no impact and another one a huge impact. Our approach was not very risk-based from an investigation perspective. And we had an NC backlog, which meant that we were not making it a priority to address the issues.

I am not going to go through each one of these (see box on p. 36), but I am going to highlight the improved management review in 2008. There has been lots of discussion about this – the ‘speak up environment,’ and the quality culture, and encouraging others to come forward to highlight issues and concerns and push them up the ladder so that everyone knows what is going on and can be on top of it.

Our management review meetings are very noisy. And they are difficult. They make you uncomfortable sometimes. And other times you walk out of them feeling like you have just finished a marathon. It is the best thing ever. That is how it should be. And when we talk about rolling up metrics, management review isn’t just looking at metrics – management review is discussing the tough things.

One of the tough things that we run into is why some people’s metrics are always green. ‘Hey Joe, for the third time this month, your metrics are green again. Is that the right metric? Are you measuring the right thing? You know, I want to hear some truth here. For some reason I am thinking that green doesn’t necessarily mean that everything is great.’

[GlaxoSmithKline Quality VP Guy Wingate] actually mentioned yesterday that this mindset and the behaviors that come with this culture is one of the elements of a holistic approach to being pro-active [in] ensuring quality.

Amgen has taken a multi-faceted approach to our investigations and improving them. You will see six buckets that I
will talk about. And as I said, it is a journey – it didn't happen overnight. It has been over seven years, and we will be on that journey for a long time. Management understands that it will cost them money, relative to the long run, but that it is going to pay back ten-fold. And we do this really, bottom line, to ensure that we can meet our goal of 'every patient, every time.' Because if we can't get product out the door, we have not met our responsibility of serving patients.

The first bucket is a risk-based approach to review errors. It is a patient-focused, risk-based approach.

You all have classifications of some sort, right? One/two/three, low/medium/high – whatever they may be. Ours are fairly simple in that they are about what the impact is to the product, which then translates to impact to the patient and what the risk is that there is going to be that impact. A Class 1 non-conformance has no impact. Are we concerned about these? Yes. We are concerned about them because they indicate that there is an issue that we want to fix. Are we going to throw all of our resources and all of our people on top of a class 1 NC? No, we are not. We are going to focus our time and our money and our efforts on the Class 2 NCs that have the potential to impact product as well as the Class 3s.

The second bucket is the technical writing training that we offer and the standardized investigation report template. It sounds simple. It says ‘training,’ like reading an SOP kind of thing. But it really is not.

We actually customized a program. We created it with the help of consultants, and it is specifically tailored to Amgen. We gave the consultants numerous investigation reports to help them understand what we do and how we do it and asked them to tailor the training specifically to our issues, our concerns, and our business – so that they could create a training program for our NC investigators. These are the folks that own the NC records. They are the people that present the investigation to auditors. They are the ones who know everything about it.

It is a two-day course. Not only does it teach basic writing skills and scientific writing, but it also teaches concepts like claims, reasons and evidence. Every time you have a claim you have to have a reason for it and the evidence to back it up. Then also things like inductive versus deductive reasoning – understanding the difference and knowing what kind of reasoning you are using in your argument.

So we are not just training people, we are educating them. Context has been mentioned in just about every talk we have had the last two days, and context is very important for these investigators to understand why they are doing what they are doing and how it is critical.

Next is our investigation report template. How many of you use TrackWise? Have you ever printed out a TrackWise report and tried to read it and make sense of it?... When I pick up a report I want to read a story of what happened. I want to have buckets of information like a scientific journal would present them, [including] an executive summary and the bulk of the information. I know where to find it. Everything is there in one comprehensive document. We couldn’t get that from Trackwise, so we used Microsoft Word.

It doesn’t matter what format you use. We wanted a format that could present the information in a scientific fashion and that could also allow us to insert graphs, charts, images, and photos – anything we needed to help make the story
more clear and to present a more robust argument.

One thing we also teach investigators is that when they are writing these reports, they have to consider the audience. If you are talking to an FDA inspector, or any regulatory agency body, and they pick up the report and they see acronyms all of the place and they hear code words for a process step, you have to make sure that you take a step back and say, ‘I am so close to this investigation. I need to take a step back and explain it to someone who knows nothing about it.’ You have to make that assumption.

Quality Sciences

So next big bucket – and this is a plug for myself – we created a team at Amgen called quality sciences. Quality is in the name, science is in the name. We do a whole host of things, but our primary responsibility is to ensure that critical Class 3 investigations are properly scoped. Once the investigators are notified of a deviation, they open an NC record. Within seven days they need to notify one of us on the team of the investigation and give us all the information they have at that point. We make sure they are on the right track with the direction they are going for the investigation. We make sure they have considered any other potential lots that are impacted by the deviation, because it may not only be just going on right there.

We also are involved in reportability evaluations: If there is product on the market that may be impacted by the deviation, we are immediately involved. We immediately gather a team of individuals to discuss what the issue is, what the potential is, and what we need to do from a communication perspective with the agency.

As a team we also run an advisory board that meets weekly, if needed. All Class 3 investigations are presented to the board. The board is made up of individuals across the network. We have global network leads to foster the communication and knowledge management and sharing. We actually have different networks at Amgen, [including] Contamination and Control, Forensics, and Bulk Production. They are all networks – individuals from every site that get together on a regular basis to discuss issues they are having, projects they are implementing, and sharing information across the ocean as necessary.

So we get those people on board. We get all the site quality heads in the meeting. All of the individual Quality Sciences team members are there. And we sit down and we discuss the investigation and where it is at that point. We don’t want to see it at the end – the advisory board is intended to advise. So we want to see it when they have enough information that they can present a reasonable story, and then we kind of tear it apart and rip holes in it.

We ask things like, ‘did you consider that you might need an HHE – a health hazard evaluation? Have you talked with the clinical immunology guys? Do you need to talk to forensics? What do you need to do with that particle ID?’ Those kinds of questions.

Another thing that quality sciences does is we run a weekly report. That NC report summarizes all Class 3s that are currently open – gives an update that goes all the way up the chain. It goes to my senior VP of quality. He forwards it on as appropriate. Basically it [addresses the questions]: ‘Do we have concern for supply? Does this deviation have the potential to impact product getting to the patient? Does it impact GMP compliance? Do we need management’s help?’ Do we need [Amgen Senior Quality VP] Martin Van Trieste to give us a call and say, ‘what can I do for you?’ That is a weekly communication that goes out to a large list of people.

Another thing that we do regarding knowledge management and sharing of information is we host quarterly webinars. The demand has gotten such that they will probably become monthly at some point. A lot of times those webinars are discussing a major class 3 investigation, and it is at the end of the wrap-up, at the conclusion of the investigation, when we share the information beyond those people that need to know ahead of time. That is handled through our alert system. This is for the layperson at the bench who runs the HPLC method who wants to learn more about a particle investigation, for example.

We are an independent organization. [FDA Consumer Safety Officer Erin McCaffery] was talking yesterday about how sometimes you can’t see the forest for the trees because you are so close. You are right there. We are kind of
that independent consultant. People ask what I do for Amgen. What site do I work for? What group am I in? We kind of get to say that we don’t work for anybody. We don’t belong to a site. We are completely unbiased and therefore we can ask the tough questions, force the tough issues, and really force people to think outside of the box.

My manager loves to say that no one ever received an award for expanding the scope of an investigation. And I think that was probably true back in 2006 at Amgen. But I will tell you now that the group is highly regarded. It is very well respected. People, and investigators in general, are learning from that. They are feeling stronger and more empowered to expand the scope, to ask the tough questions, and to really push their management to say, ‘maybe we really do need a piece of equipment that costs a million dollars. And if you can’t do that for me, you have to tell me what is going to address the risks involved in not doing it.’

So the scope check is the big piece when it comes to Class 3 NCs that come to us. There are only eight of us. We are geographically distributed – there is one of us at pretty much every Amgen site so that we do have direct face-time if needed. They also ship us all over as needed.

We have lots of expertise on the team. We have a couple of ex-FDA folks, although when I call them ex-FDA, it feels like a divorce. Should I say former FDA? ‘Ex’ just sounds so permanent. We have others with a lot of regulatory experience, and yet others like myself – I come from an analytical background. So we kind of run the gamut. We also know that when a new investigation comes in, if we have a person with that expertise we will ship it to them so they are the first person involved.

**Causal Factors and Root Causes**

If you will recall, this was number two of the key points to take home. This is a lovely tree, and trees have two parts to them. The pretty part that you see that helps provide the shade that turns orange in the fall, and then you have the roots that you don’t really see, but they are so important because of how they hold that tree in place. Causal factors are the leaves – it is what is obvious. It is the action or the lack of action that contributed to or caused the event or

![Causal Factor vs. Root Cause](image)

**Causal Factor**
Immediate or apparent factors associated with an event that caused the event to exist

**Root Cause**
Underlying deficiencies in the policies, procedures, training, expectations and communications that allowed the Causal Factor to exist

**Example**
Incorrect hose connection led to product loss

Hose connection diagram unclear, and hoses not properly identified

Casual factors disguised as root causes will lead to ineffective CAPAS
made it worse, and it had to be present for the event to occur.

Here is an example – not my example, but it works. The hose is incorrectly connected to the tank and you lose product. That is the causal factor. Most people stop there. ‘What are you going to do to fix that?’ ‘I am going to correctly attach the hose.’ Great. ‘How are you going to prevent it from happening in the future?’ ‘I am going to make sure I train that manufacturing operator that he has to make sure that hose is attached every time.’

The root cause is one step further. The root cause is what allowed or failed to prevent the causal factor from happening. When that operator went to connect the hose, the diagram wasn’t clear in the procedure. Or the hoses were not properly identified. Maybe there were two hoses that looked similar. They are both there on the shelf to use, and it is not clear which one, so you throw one on there.

How do you fix that? Well, it is not retraining the operator. Fixing that is getting to the underlying deficiency in your procedures. Maybe it is training. It is expectations. It is understanding. It is the context behind what that hose does and why is the connection important.

When you do this well, it is very effective in creating your CAPAs to then correct issues and prevent future issues from happening. It helps structure the investigation. The light bulb goes on and you see the light at the end of the tunnel. It is very clear what you need to do to fix something. But when you do it poorly, you get bad CAPAs that are not effective and you are back in that cycle of it happening again…. 

In standardizing your root cause analysis process, [be careful of] tunnel vision or siloing. You walk into a conversation and the first thing a person says is, ‘well, I am pretty sure that this is the problem.’ So everybody focuses on getting information that supports that assumption. Where is the disconfirming information? What are the other possibilities? Think outside of the box. Avoid the need to have a most likely root cause while you are going through this process, the analysis process, because it will pigeon hole you in and won’t let you see what is going on.

Once you have found all of the causal factors – because there usually are more than one that kind of converge to cause the event to happen – then you can break it apart to see what really contributed. What things needed to happen for that event to exist? Why did those things exist? And how do we correct those? Once you have determined all of the root causes, then you can focus on the most critical ones – the ones that require implementation, the ones that are going to give you the most bang for your buck. Then you do what you can to fix the problem. And if you do all of this – I love [Quantic Group President Claudio Pincus]’ phrase yesterday – ‘you get it right the second time.’

Certified Investigators

The fifth bucket of our program is something that most people are usually interested in. When you talk about training someone at your company, the NC owner needs training on the database that they are going to document in. Maybe they read a couple of SOPs. Maybe you give them some root cause training, that type of thing.

At Amgen, we have moved to a program where we actually qualify and certify our investigators. It starts with the foundation, and this applies to Class 2 non-conformances. All Class 2 NC owners are qualified. When you are qualified, what that means is that as soon as someone decides that you are the right person for the job, you are assigned a mentor. The mentor is from leadership somewhere in the company, usually within your own functional area, but not always. And they are someone that invests a lot of time and effort into walking you through this process and helping you grow and develop as an investigator.

We recognize that this job is not easy. NC owners get push back from everybody. Everybody is pounding on their door. Supply chain wants to be able to disposition. They want to release the lot. They want to ship it tomorrow. The quality unit wants to meet its metrics for NC closure. Engineering wants to get the equipment back in use. It is not an easy job. And if you just throw someone into it and you say to them, ‘good luck, and by the way, you are kind of just an average employee,’ they are not going to stick around and they are not going to do a good job.

At Amgen, NC investigators are highly regarded, very well respected, treated very well, and they have become not the
'whipping boy' anymore, they are now kind of more the 'golden child.' And it is recognized that it is not easy. And for that recognition, you will see comes the next step of certification.

But also I think it was Veronica talking about needing to have the right person in the right job. Not everyone can do this. And you have to be able to recognize when they can't and move them on to something else.

Class 3 NCs are a whole other level. [They receive] additional training, including project management. Some people say, ‘project management, why do they need that?’ A critical, complex investigation, is a project in and of itself. There are so many people you pull together. There are so many different elements. There are so many people you need to touch. You need to have good project management skills and communication skills to make that all happen, to make it work. So that is part of the training that we require.

And then for Class 3s, investigators are certified. Certified means you have gone through a very formal process. You have presented to a board. You have had investigation reports reviewed by numerous mentors and graded with our rubric, which I will explain in a minute. And it is not easy. We have had people fail this and not become certified.

The Rubric

I mentioned the rubric. The rubric is Amgen’s attempt to measure the quality of an investigation. It is pretty much our first big attempt. So far it is working pretty well. We are tweaking it as we go along and learn more about it. I think all of you can agree that it is difficult to measure the quality of an investigation. One of our previous metrics was number of days to the NC closure. That tells you nothing about quality, other than if you rushed it, you probably don’t get the quality that you want. But, ‘hey, I closed it in 30 days.

The mentors use this rubric, which as you see has various buckets. The most heavily weighted is the reasoning and evidence piece, because that really is the meat of the investigation report – that is where all the critical information goes.

The middle tier is on completeness, organization, and ease of finding key points. If it is not complete, if it is not organized, is not logical, and doesn’t make sense, no one is going to be able to read it and understand it anyway. So even if you have everything on the bottom, it doesn’t matter if you do not have the stuff in the middle.

At the top, you have to have good punctuation and grammar and all that good stuff. Everybody knows that first impressions make a difference. So if I am reading a report and I see misspelled words and formatting issues, I immediately think, ‘who really looked at this closely? Who really made sure that this has what it needs to have?’ So it is part of the rubric. This is part of our attempt to measure it and standardize it across the company.

Here is an example of one of the pages of the rubric, used to grade the reasoning and evidence portion of it. What you will see is it is not just ‘did the investigator dot the I’s and cross the T’s.’ There is also a piece on reasoning and logic – for example, does it include: ● claims, reasons, and evidence ● the proper scope, and ● justification for the
scope of the investigation?

To the left we have the ratings. They are in big chunks. We are not going to split hairs over one or two points there. It is either there or it is not. So we kind of did that to help simplify the process as well.

**Results and Conclusions**

I am almost out of time, but I am going to quickly summarize and show you what it has done for Amgen.

There are six big buckets we have been implementing over the last seven years. This is what we have found in success with it…. Since 2006, we have decreased the number of *errors per lot* by 95%. It is huge. Think about that. If you can reduce the number of errors per lot, what else do you do? And $150 million – the big guys like to see that $150 million savings.

So the other thing we did is decrease our *disposition cycle time*. For my senior VP [Martin Van Trieste], his number one most favorite metric is disposition cycle time, and that is because you can’t hide in that metric. It really tells you about the health of your process and your entire system. And sure, you can manipulate it a little bit, right? Like, ‘hey, we need to disposition this batch tomorrow, throw five more people on the review of the record.’ But you can only do that so often. If there is an elephant in the corner, those five people can’t do anything about it. We have decreased our disposition cycle time for both drug substance and drug product, spanning all of the sites across the network.

This is the one that you take to your upper management and say, ‘this is why improving our investigations is good for business – 92% reduction in scrap.’ That is huge. Who is not going to love to see that? And what it tells you is quality really is free if you get it right.

We did all this while we encountered all of the same issues that you do. You know, the ‘do more with less, be lean, be more efficient, save us money,’ all of that good stuff. We did it while doing all of those things. At Amgen it has been a lot of years of change for us. And we are proud to say that we have supplied ‘every patient, every time.’ We are only one of two companies that have been able to make that claim. Everything I do every day is to continue to be able to make that claim.

In closing, it is all about sustaining and maintaining. Do not let your guard down. You have to be diligent. You have to stay fully committed to the program. It has to be a life-style change. It cannot be just a diet. You have to remain proactive in how you approach these things.
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Updates in Brief

UNITED STATES

CMC/REVIEW

FDA Launches "openFDA"

In early June, FDA launched openFDA, an initiative to make it easier for web developers, researchers, and the public to access large, important public health datasets collected by the agency. Currently, information from the FDA Adverse Event Reporting System is available, but the initiative will soon include datasets on drug labeling and recalls. [For more on FDA’s transparency initiative see p. 19.]

FDA Issues GDUFA Payment Warning Letters

In early June, FDA issued the second and third warning letters to companies that failed to pay their GDUFA user fees. The first came in September of 2013. [See IPQ “Monthly Update” September 2012, pp. 44-45 for more on GDUFA user fees.]

Guidances Issued on Nanotechnology Products

In late June, FDA issued three final guidances, and one draft guidance, to clarify the use of nanotechnology in agency regulated products. The guidance “Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology” explores the boundaries of nanotechnology and how it is defined. The “Guidance for Industry: Safety of Nanomaterials in Cosmetic Products” focuses on the safety and behavior of new nanomaterials. The third final guidance covers the use of nanotechnology in food products, with the fourth, draft guidance in the series covering animal food use. [See IPQ “Special Report” May 2010, pp. 54-61 for an in-depth review of the goals of FDA’s nanotechnology initiative.]

FDA Releases Guidance on Q4B Evaluation

In mid-June, FDA announced the availability of a final guidance entitled, “Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the International Conference on Harmonisation Regions; Annex 6: Uniformity of Dosage Units General Chapter.” The guidance provides evaluation results from the ICH Q4B General Chapter harmonized text and is in the form of an annex to the core guidance on the Q4B process entitled “Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions.”

Aurobindo Notifies FDA on 86 ANDA Withdrawals

In mid-June, FDA announced the withdrawal of 86 Aurobindo ANDAs, following the firm’s notification to the agency that it was no longer marketing them and its request for the withdrawals.

GMP/INSPECTION

GMP Warning Letters Continue to Compounding Pharmacies

In June, two more compounding pharmacies received warning letters from FDA – Sunnymede Pharmacy, doing business as Lee and Company and Lee Pharmacy, and Pharmacy Creations. Both letters include citations involving contamination SOPs and environmental monitoring – the most common problems FDA is finding at sterile compounding facilities. [See IPQ “Monthly Update” March/April 2014, pp. 36-39.]

Two Foreign API Manufacturers Issued Warning Letters

In June, Apotex and Tianjin Zhongan Pharmaceutical received warning letters addressing API manufacturing issues. Apotex was cited in its letter for data integrity issues at its facility in Bangalore, India, based on inspection findings in late January. The inspection findings resulted in an import alert being placed on products from the facility in April (see IPQ “Monthly Update” March/April 2014, pp. 19-29). Among the issues noted at the Tianjin, China plant for Tianjin Zhongan was inadequate change control.
U.S. Wockhardt Plant Receives 483 on Data Handling

In late March, FDA issued a 483 to a Wockhardt facility in Morgan Grove, Illinois for lab data handling issues similar to those found at the firm’s facilities in India (see IPQ “Monthly Update” March/April 2014, pp. 19-29). Of primary concern in the 483, as at the Indian facilities, is the use of “trial” testing and the lack of lab data retention.

FDA Issues Draft Guidance on Identifying Suspect Drugs

In early June, FDA announced the release of a draft guidance for industry on “Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification.” This is the first guidance issued under Title II of the Drug Quality and Security Act (DQSA) (see IPQ “Monthly Update” January 2014, pp. 13-20). It advises drug supply chain stakeholders on how to identify suspect drug products as well as how to notify the agency of illegitimate drugs. The draft is open for comment until August 11, 2014.

FDA and Customs Announce “Trusted Trader Program”

In mid-June, FDA and the U.S. Customs and Border Protection (CBP) announced the launch of a new “Trusted Trader” program meant to expedite the import of products made by companies that are known to meet a quality selection standard. Participants in the program will be given incentives such as exemption from “non-intrusive” inspections. To qualify, participants must meet all FDA and CBP regulations and laws, release import records to the CBP, and develop an internal risk assessment plan. The test program will last 18 months, starting June 16, 2014, and is open to no more than 10 participants. In February, FDA launched a “Secure Supply Chain” program pilot, which allows participating companies to import up to five products with expedited clearance (see IPQ “News in In Brief” February 20, 2014).

ISPE Launches Quality Metrics Pilot Program

In mid-June on its website, as well as at the early June ISPE/FDA CGMP Conference, ISPE announced the official launch of its Metrics Pilot Program. The pilot is open to any drug manufacturing company registered with FDA. Primary objectives of the program include working toward harmonizing definitions around leading and lagging indicators, and testing the feasibility of metrics data collection within and between companies. [See IPQ “Monthly Update” June 2013, pp. 12-20 for more on the industry/FDA metrics discussions.]
Sustainable compliance demands a proactive approach

A proactive approach to achieving and sustaining compliance is ideal. But, if the unforeseen occurs, you need to make well-informed decisions to overcome a product crisis.

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Revised EMA Guidance on Advanced Therapy Classification Out for Comment

In late June, EMA released a revised version of its “Reflection paper on classification of advanced therapy medicinal products.” The revision provides further clarification on when medicines may be classified as ATMPs and when they cannot. Clarification is added on: ● what constitutes a substantial manipulation of cells or tissues ● what is considered a non-homologous use of cells or tissues ● when medicines based on recombinant viral vectors are considered as vaccines, as opposed to gene-therapy products, and ● the criteria for classification of combined ATMPs, i.e. products that incorporate an active substance and one or more medical devices.

EMA Revises Guideline on Quality Issues for Biosimilars

In June, EMA released a revised guideline covering quality issues for biosimilars using biotechnology-derived proteins. The guideline covers the quality requirements to be met when developing a biosimilar. It follows from a concept paper from 2011 and a draft from 2012. The revised version contains references to relevant guidelines that should be consulted and an expanded section on what reference products are applicable.

EDQM Publishes Annual Report for 2013

In mid-June, EDQM published its 2013 Annual Report. The report explains the function of the EDQM, its relationship to the European Pharmacopeia, and the major changes that took place within the directorate during 2013. Some highlights include the adoption of 30 new monographs, the addition of 2 new general chapters, and the modernization of quality standards.

EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) Issues Final Opinion on Nanosilver

In mid-June, the EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) published its final opinion regarding the safety of nanosilver and its role in antimicrobial resistance. The opinion summarizes the ways that nanosilver is introduced to both individuals and the environment, its benefits as a method to introduce silver to organisms in soil, water, and sediments, and the need for more study on how microbial resistance responds following exposure.

GMP/INSPECTION

EMA Releases New Guidance and Template for QP Declaration on GMP Compliance of API Manufacturers

In late May, EMA issued a guidance and a template for Qualified Person (QP) declaration of the GMP compliance of API manufacturers. The template is designed to standardize the format of the declaration and reduce the number of follow up questions. The agency recommends its use to “facilitate the validation of regulatory submissions and their review.” EMA issued a draft revision of EU GMP Annex 16 on QP batch release in July 2013 (see IPQ “Monthly Update” March/April 2014, pp. 19-29 & July/August 2013, pp. 23-30).

EU Launches Genuine Online Pharmacy Logo Scheme

In late June, EC introduced a logo that will allow patients to identify authorized online pharmacies providing authentic medicines.

EMA Removes Ranbaxy API Plant from Ban

In early June, EMA announced that a reinspection of Ranbaxy’s Toansa, India API plant revealed a number of GMP deficiencies, but no risk to public health, and that the import ban placed on it was being removed. The FDA import alert remains in place after the agency’s follow-up inspection of the plant in January (see IPQ “Monthly Update” March/April 2014, pp. 19-29).
WHO Releases Storage/Transport Supplements

WHO has released for review a set of supplements on its Technical Report Series, No. 961, 2011 Annex 9, which provides a “model guidance for the storage and transport of time and temperature-sensitive pharmaceutical products.” The supplements cover:

- temperature and humidity monitoring systems for transport operations
- temperature and humidity monitoring systems for fixed storage areas
- design and procurement of storage facilities
- maintenance of storage facilities
- selecting sites for storage facilities, and
- estimating the capacity of storage facilities.

African Medicines Regulatory Harmonization Program Announces Centers of Excellence

In mid-June, the African Medicines Regulatory Harmonization Program (AMRH) announced the establishment of new centers for excellence for regulatory training. According to the New Partnership for Africa’s Development (NEPAD), an arm of the African Union (AU), these institutions will play an important role in increasing the regulatory capacity of Africa as a whole. The role includes participating in increasing and improving the regulatory workforce in Africa through academic and technical training in regulatory science.

TGA Update on eCTD Submissions

In late June, TGA provided an update on the progress it has made in being able to accept electronic versions of common technical documents (eCTDs). The agency announced its agreement to purchase software in late February, and has since revised its Common Technical Document Module 1 to further its alignment with the European eCTD. TGA will soon be looking for pilot submissions from industry to test the new system before its official launch in early 2015.

TGA joins EDQM’s CEP Assessment Process

EDQM announced in late June that its CEP Steering Committee has accepted the request from Australia’s Therapeutic Goods Administration (TGA) to actively participate in the assessment of applications submitted by manufacturers desiring a CEP. TGA has been accepting CEPs approved by EDQM for the past few years.

EDQM Signs Confidentiality Agreement with Taiwan FDA

In late May, EDQM signed a confidentiality agreement with the Taiwan FDA. The confidentiality agreement concerns the “certification of suitability to the monographs of the European Pharmacopoeia,” and includes communications about the quality assessment of APIs and excipients used in manufacturing as well as about GMP inspections of manufacturing sites.

PDA Releases Revised Technical Report 13 on Environmental Monitoring

A revised version of the PDA Technical Report 13 was released in late May. This technical report serves as a resource on controlled environmental test methods for sterile product manufacturing. The revision updates the previous 2001 version, reflecting the changes to regulatory guidelines, international standards, and scientific advances in environmental monitoring. The report is available as a free download to PDA members until the end of July.
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