

What I would like to do today is to share with you where we are and where we are heading. What I'm sharing with you is a roadmap into the future. Without any exaggeration, I think we are changing the paradigm of how to assess quality of pharmaceuticals in the U.S. and in the world.

I'm going to share with you where we are, why we are changing, some of the high-level thoughts, and by the end of my presentation and Gary Buehler's presentation, our combined effort, hopefully we'll illustrate to you where the Agency is heading. And then we can open the floor for discussion and seek your input.

I will appreciate hearing from you all after my presentation because we are working at a very fast pace in order to make this change happen. And we would like to make this happen in a matter of weeks and months, not years and so forth.

These are the topics that I will try to cover within 25 minutes but Gary and I have an hour so I may use a little more time, Gary.

I would like to share with you where we are. I would like to update you on what we had before, which we called the CMC risk-based approach or initiative. I want to tell you that we are changing from chemistry review into a new quality assessment paradigm and describe to you what I mean by that.

I would like to summarize in a few slides the difference that I see between chemistry review and the quality assessment. And I would like to share with you some of our pilot programs and supplement review and so forth.

CMC review, as we all know, is intended to assure the identity, purity, quality, and strength, an potency as related to safety and efficacy for drugs throughout their life cycle from IND to NDA, most of all through the ANDA process.

This is an organization chart of ONDC. You see how simple it is. We have about 130, 135 review chemists and scientists spread out through 19 chemistry teams co-located in 15 clinical divisions. It's very difficult to manage such an organization. We are not managing well.

I hope in the future when I come next time, if Ajaz invites me, to share with you our new organization and how it will not only compliment the future product assessment but manage the losses within the agencies much better than it's being managed today.

This illustrates how much work we do in the office. The in the last fiscal year, we reviewed 159 NDAs. We had close to 1,000 INDs. We had about 2,000 supplements. That's a lot of work. And if continuing in that direction, we are going through a viscous cycle for when every time we approve a drug, the number of the supplements increase, our workload increases, and we create a problem not only for ourselves but for efficacy in the public as well. And there is a crying need for a change.

To summarize our current CMC review practices, when it comes to the application that we receive, the quality of this application varies considerably. Some are much better than others.

The applicants don't always seek consultation and meetings through the review process or follow some of the recommendations that we make and agreements we make during the review process and during the submission.

And sometimes they have, sometimes they don't have, but in many cases they do not provide enough pharmaceutical development information that I consider to be essential in order for us to do what we call risk-based CMC review.

What about our review? We evaluate all CMC information and data that comes in the application without doing too much as far as differentiating between what is critical and what is less critical.

We evaluate all the information that comes to us. And that evaluation does not necessarily utilize the vested training and background of our reviewers. Basically we have one CMC reviewer, for most part a chemist, who conduct the entire evaluation.

And if you don't have enough knowledge, they try to do the best they can. They are trained while they are doing the review. And there is good mentorship throughout the process. It's a value list-based review. I think someone today called it a check-list review. It's not really a check-list but it's a value list-based review.

We don't do enough in-depth review of process information and that's in part not totally because of the center field agreement. We have tight specification, I have to admit to that. But the specifications are set based on the limited data we receive.

This is the information we get, and based on that information, we set the specification with our goal is to assure that consistency of manufacturing process. So basically the specification is a way to control the manufacturing process.

Often we have late and voluminous CMC amendments that lead to delay in review. And as you all know, we have problems with the cycle of review and approval.

The decisions are made based on submitted data and the individual experience. There is a lack of critical information pharmaceutical development. Guidances, for the most part, are established to provide regulatory relief but at times create an increased number of supplements and that creates problems for us at the agency and for industry as well.

What are the problems with the current system? For us at the agency, it is very resource intensive. You have seen our organization chart and you see the workload. We have to deal with recalls and drug shortages at times.

For you all in the industry, there's a perception that because of the existing regulatory system, it discourages continuous improvement. Regulatory burden, what's the value of all the supplements and all the review we do? And what are the consequences of being out of specification that require investigation, recalls, 483s, warning letters, and so forth.

What about the public? High cost drugs maybe and delay in drug approval at times.

In the middle of this, with all what we are doing, with all the problems, we are facing some major challenges. In trying to outline these challenges in this slide here, we have the GMP initiative which, I think, many of us agree is really a product quality initiative for the 21st century.

How can we fit the existing regulatory system into the new way? How can we do that? There is a conflict. How to deal with first cycle approval? The heavy workload. How can we address the consistency issues and problems and difficulties that exist among the 19 chemistry teams in 15 clinical divisions?

We are attempting to do that through the guidance process. It helped some but created different kind of problems.

We have problems with the guidance and policy development. There is a lack of expertise in many critical CMC areas, many sites of pharmaceutical development. We are dealing with novel, new delivery systems, combination drug products, new technologies.

Because of all these, what we have done before and attempted to do it with some success is react rather than have a proactive proposal of how to deal with issues in the future.

I want to spend a couple of minutes talking to you about the standards of the risk-based CMC initiative that started in the year 2000 and went on until last year when I came here to this shop. That initiative was evolved over many years.

It's multi-tiered. If you look at the initiative, it was outlined as a three-tiered process. When everything was said and done, it was a five- or six-tiered because every tier split into two sub-tiers. We would start with Tier 1A and talk about three years. So if you go through the five-tier process, it would have taken us many, many years. That's okay.

The whole initiative was product specific. It addresses and deals only with what we are very comfortable with and that's mainly synthetic drug substances. Characterization must be done using traditional analytical techniques that you can clearly see. It applies only to very specific products such as immediate release or dosage and so forth.

That initiative was intended to provide regulatory relief by incorporating science-based and risk-based assessment in CMC review. But one thing that became obvious with the GMP initiative is the relevance of that initiative with our new product.

This is something that we have to deal with only for a small class of drugs and in very special cases or if there is some merits for better utilization of science- and risk-based to apply that for everything we do, from that pre-marketing into the post-marketing.

So now we are dealing with more progressive and expanded initiative that was focus on the totality of quality assessment. The risk-based quality assessment has a variety of advantages. And what I have done in these two slides is summarize some of the excellent findings that were obtained after the PQRI Conference about a year ago. The PQRI Conference that Toby Massa co-chaired.

The benefits of the policy assessment risk is the quality assessment for the patient for the increased availability, faster approval, and the patient will continue to receive our quality products. So we are not going to sacrifice the product by -- that may result from a reduction of regulatory oversight. It's basically more focused on our regulatory process rather than reducing regulatory focus.

For us at the Agency, there will be more product and process knowledge that is shared by industry, more efficient resource allocation, increased trust and better communication. And for industry, there will be more efficient science-based inspection, faster -- and you will hear more about that. I think David Horowitz will talk to you all tomorrow about the new paradigm in GMP inspection.

There will be faster, more consistent review, a potential for reduced regulatory burden, ability for you to manage the changes without very strict regulatory oversight from the Agency, focus our resources on critical issues, flexibility to focus on what should be done not what can be done, improved communication with the Agency.

And I think that the striking element of what we are trying to do today is if you look in the past, the Agency changes regulation. The industry we had. The industry raises the bar because of new delivery system and newer technology. The Agency react. But in this new paradigm, we are working together in order to head in the right direction.

When we talk about the new quality assessment paradigm, I would like to make clear to everyone here today that this is not a single initiative to address one dimension of a multi-dimensional, often complex quality assessment process. This is not a streamlining effort.

It's a new paradigm of quality assessment for new drug applications. And Gary will share with you his thoughts about generic drug applications as well. But that covers for the new drugs the entire or the totality of quality assessment from pre- to post-marketing activities.

With that we have to change our vision and our mission. And that is part of where we are heading with our new organization. I'm going to focus here on a couple of things because I think -- I do believe that the vision and the mission should clearly indicate to us, to our staff and to the public, where we are heading.

Our new vision indicates very clearly that this is a scientific organization that services the center, the Agency, and the public through leadership and innovation and international collaboration. I do believe in international collaboration. I do realize that we are dealing with global industry. And our efforts here have to be done under the umbrella of harmonization with other international agencies.

As far as our mission, we no longer continue to do chemistry. What we will be doing is for our office to assist the critical quality attributes of manufacturing processes for new drugs, establish what is the standards to assure safety and efficacy and -- and that's very critical here and that's why we need to work together to be a partner to facilitate drug development.

Some of the future elements that we need to work on and we started working on our assessment will start with a comprehensive quality overall summary. And I think you had some questions and some comments about that this morning. And that is something that we need to work on.

Review practices should be based on good scientific principles. There will be considerable increase in emphasis on manufacturing science. The CMC review and the quality assessment functions we do will be critically reviewed by our colleagues and staff and scientists at the Agency. And we must integrate our review functions with the inspection. And that goes under the umbrella of Q8, !9, and potentially Q10.

When it comes to CMC's specification and there will be another time for a larger group for another discussion about how we set the specification and why we set it and how it should be set but the main principles are specification has to be risk-based -- based on risk-based assessment, clinical relevance, safety considerations, process capability, knowledge gained from pharmaceutical development reports, and better utilization of modern statistical methodologies.

There is such a thing as regulatory relief. Such relief will be provided based on the following three criteria.

One is process understanding and control. And that what you can share with us through the pharmaceutical development reports, assessment throughout the manufacturing process, and your ability, because of your understanding of your process, and your plans to continue to improve the process. So these are three criteria that has to be there in combination in order to provide an assurance of your ability to continue to improve the process. One of these elements by itself is insufficient.

Pharmaceutical development reports may facilitate meeting for a cycle approval, science-based specifications, risk-based GMP inspection and regulatory relief from post-approval activities.

What we do at the Agency is done by people, not by machines and computers only. And that's why it's very important that we invest in our staff and provide the correct work environment and resources to support our staff. So it's very important for us to provide better work environment to our staff to facilitate superior performance and job satisfaction.

During the CMC restructure, we are in the process of reorganizing the office. The reorganization is intended to facilitate the implementation of the new quality assessment paradigm. What I'm saying is we are not moving 15 or 19 offices from one place and put them in another place. The organization will be there for one purpose and that is to facilitate the new paradigm and to facilitate the implementation of the new quality assessment.

I may come back to you later on on this one but I just want to give you heads up. We are considering establishing a CMC Scientific Advisory Board and some of the functions of this Board would be to provide scientific consultation when needed.

There is no way we will have enough expertise in house to address every regulatory or scientific issue we deal with. The Board will oversee the ONDC regulatory research program, restructure and modernize the ONDC training program, and also develop regulatory science seminars.

We are in the process of recruiting and hiring and training pharmaceutical quality assessors with expertise in drug discovery, analytical chemistry, pharmaceutical development formulation, and pharmaceutical engineering. I think there are so many people here in this room, if you know of anyone whose is looking for a challenging opportunity, I'm all ears.

(Laughter.)

DR. NASR: We have several vacancies both in the review side, on the technical side, and in management as well. And I'm serious of inviting you to help us help yourself by sharing some of the talent that is out there that we need in the Agency.

ONDC is building a strong and independent scientific organization to better serve the public and our internal stakeholders. And if you see where we are today, we are co-located with the 15 clinical divisions.

Linkage with clinical division is very important but it is one of many linkages that must be there in order to assure appropriate quality assessment. So we will maintain the linkage with our clinical colleagues but we will have to work closely with our colleagues in the Office of Compliance and the Office of Generic Drug as well. And with industry and other scientific organizations.

Our re-engineering effort is intended to work on problems that have been identified in order to meet expectations and to establish a modern equality with appropriate metrics to measure the quality of CMC review and performance.

This is very important here and we are working very hard to do that. It's very easy to have metrics to count beans, how many reviews, how many supplements, how long it takes you to do that. But we need to identify the appropriate metrics to measure the quality of the work we do and that input of our review into drug development. This is something we need to work on.

Before I go to these two slides, I'd like to remind you all that we have a very large quota of competent, dedicated, hard-working scientists. But what I'm sharing with you today does not necessarily indicate in a negative way that our organization is not functioning well. But we are shifting our paradigm.

So I want to describe to you where we are today and where we are heading. And I think I can best describe that in these two slides.

Here is what we do today. What we do is chemistry review. This is not something -- I've used a term that I intended that everyone is using that term around the agency. The review is conducted by chemists. There is extensive data analysis in order to generate the necessary knowledge and summary reports of CMC issues. That's what we do.

We get a lot of raw data, stability data, validation data. We use -- we review everything that is submitted to us. And generate summaries in order to be able to have a story to tell about the product itself.

One would question is it us who should be developing this story or is it the industry or the sponsor who developed the product that they can come and tell us their story?

It's a guidance-based review. There is more focus on chemistry and specification issues and there is less focus on process and manufacturing. There is no clear emphasis on what we consider to be critical CMC issues. We do not have a peer review process to evaluate the quality of the work we do at the center or in the office.

Quality assessment is a very different thing, assessments conducted by interdisciplinary scientists, chemists, pharmacists, engineers, and others as needed. There is more reliance on knowledge provided by advocates and that includes pharmaceutical development report and comprehensive quality overall summary.

It's a risk-based assessment. It's not everything. Focus on critical quality attributes and developments to safety and efficacy and these are some of the critical attributes that we must focus on. It's a question-based review and there is a greater utilization of peer review process.

I want to spend the next two slides to briefly summarize where we are with some of these changes we are making. You will hear tomorrow from Steve Moore, a team leader in our office, talking about comparability protocol.

I think comparability protocol can serve as a bridge or linkage between the existing system and the new quality assessment paradigm. And that's why it's taken us more time in reviewing the comparability protocol guidance before we put it out because when we put it out, we want to make it more useful and more meaningful and to facilitate the changes that we are all trying to achieve.

Comparability protocol utilizes and applies quality by design principles. It should facilitate continuous improvement with risk regulatory oversight from the Agency. It provides scientific basis for expecting, understanding, managing, and addressing changes.

It brings more focus of what is critical and what is less critical. It has a great potential for down-regulating CMC supplements. The bottom line is with the workload that I described to you earlier in the first few slides, we can no longer continue to have a quality review of the large volume and that application information we get within the existing system we have.

We are exploring ways not only to down-regulate but potentially eliminate certain types of CMC supplements that have many potential to adversary effect on identity, quality, purity, safety, strength, and potency as they relate to safety and efficacy. So we are looking why do we have supplement? What role they serve?

ONDC is developing in our new organization ways to manage the supplement review more efficiently to facilitate continuous post-marketing product improvement and to provide more resources for new NDA review. I think if we understand what you are doing and you share with us your understanding, and we'll do that at the pre-marketing stage, we have great confidence in your ability to manage your own change.

You can go ahead and manage that. That will provide more resources for us to be more of a partner during drug development.

We have a pilot program for resubmitting the NDAs because we have to find ways to reduce the resources and put the resources where they are the most needed where a single CMC reviewer perform initial assessment. Initial assessment is being done in two weeks. And relevant material are requested.

An assessment protocol is developed and then assigned to a primary reviewer. A primary reviewer will perform an in-depth assessment as always done.

Streamlining of resubmission will provide more resources for our original NDA review. Where I'm coming from is this, if from direct resources and have enough and correct and enhance the level of communication with the sponsors, that may lead to first cycle approval and potentially a decrease of the number of resubmissions.

And this slide here, this is my summary slide, this is my last slide, what I have here on the left are some truths. These are truths. We are working on re-engineering supplement review, streamlining our review of resubmissions, talking about quality by design for pharmaceutical development reports, comprehensive quality overall summary.

The re-engineering of the supplement will provide less regulatory oversight for post-marketing approval changes and that may lead to more incentives for continuous improvement. The same thing with the other tools. They will provide more resources. They will enable us to do risk-based assessment. And there will be less review time.

And all this will lead or may lead to first cycle approval of new drugs. And putting all these things together, what we will end up having is at the end better product available at maybe less cost.

I think I missed one slide. My last slide that you didn't see, I would like to acknowledge Dr. Janet Woodcock and the Steering Committee for providing a lot of insight, Helen, Ajaz, Chi-Wan, and Guirag Poochikian for providing considerable input in this presentation.

Thank you.
(Applause.)