CMC Strategy Forum Europe: Life Cycle Approaches for Specifications

The first CMC Strategy Forum Europe, "Life Cycle Approach for Specifications," was held on 8 and 9 March 2007 in Brussels, Belgium. The purpose of the forum was to provide an open discussion on the life cycle approach to setting global specifications for biotechnology-derived products. Presentations by representatives from worldwide regulatory agencies and from global industry focused on implementing ICH guideline Q6B and on statistical considerations in setting specifications and were followed by industry case studies. A major feature of the meeting was its many open-forum workshops, which addressed the following key elements and challenges on the process of setting specifications:

- Applications of Quality by Design (QbD) concepts in selecting critical product quality attributes
- The role of action limits versus specifications
- The process of setting the acceptance criteria; in particular, understanding clinical experience, manufacturing consistency, and statistical considerations
- The use of a two-tier specification system (release versus shelf-life)
- Efforts toward global harmonization

The organizing committee planned for regulatory and industry experts to actively participate in the workshops by sharing specific case studies, practical concerns, and limitations typically encountered in the process of establishing specifications.

Speakers during the morning plenary session of 8 March included Pierette Zorzi from Agence Française de Sécurité Sanitaire des Produits de Santé (the French Health Products Safety Agency, AFSSAPS), who spoke about the European Union (EU) perspective on product specifications; Keith Webber of the Center for Drug Evaluation and Research (CDER), who presented the FDA's perspective on product specifications; and Robert Garnick from Genentech, who spoke about Industry's perspective on product specifications. A panel discussion followed, with Zorzi, Webber, and Garnick responding to questions from the audience.

Lifecycle Approaches for Specifications

Pharmaceutical quality is the state of having an acceptably low risk of failing to achieve the desired clinical attributes. Product quality involves assurance of the quality of both unit dose — active pharmaceutical ingredients (APIs), excipients, containers, and so forth — and batch or lot quality, which can vary. Product quality is defined by the intended purpose of the drug, the functions required of the drug, essential attributes, and both drug substance and drug product specifications. Assuring batch or lot quality includes process design — encompassing raw materials specifications and in-process specifications, a company's quality control system, and its quality assurance system.

The International Conference on Harmonization (ICH) defines "specifications" in ICH Q6, which provides similar definitions for specifications with regard to new chemical entities (NCEs) and biological products. For NCEs: "A list of tests, analytical procedures, and appropriate acceptance

criteria." For biologics: "Specifications establish the set of criteria to which a drug substance, drug product, or materials at other stages of its manufacture should conform to be acceptable for its intended use." Some of the concepts and technical requirements are different, however.

Specifications vs. Action Limits

During clinical development, specifications focus on assurance of patient safety and dosing precautions and accuracy. As stated in 21 CFR 312.23(a), IND content, "in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug." It further states that "final specifications for the drug substance and drug product are not expected until the end of the investigational process."

Specifications will change during the course of a drug lifecycle, from clinical development to marketing application and beyond. Choosing meaningful specifications requires knowledge of the product's structure-function relationships, degradation pathways, and potential process-related impurities. Specifications are one part of a total control strategy designed to ensure product quality and consistency. They are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization and should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.

Acceptance criteria have to be established and justified. They should be based on relevant development data (e.g., characterization, validation), several lots used to demonstrate manufacturing consistency, data from stability studies, and data obtained from lots used in preclinical and/or clinical studies.

Action limits are part of an in-process quality control system. In-process controls provide assurance of conformance to specifications as opposed to end-product tests because of the potential for lot variability. Improvements in lot or batch quality may be achieved without changing specification.

Changing Specifications, Changing Expectations

From the beginning, Biotech ICH discussions and guidelines focused on manufacturing processing key points. Those include genetic stability (Q5B) including control at the nucleic acid and/or protein level. Q5D considers cell substrates and quality requirements for master cell banks (MCB), working cell banks (WCB), and end of production cells (EoPC). Viral safety, discussed in Q5A, is based on in-process controls and validation.

In Quality by Design (QbD), specifications ensure that the product does what it is supposed to do. Within a QbD framework, critical quality attributes (CQAs), critical process parameters (CPPs), and clinical experience all contribute to the setting of specifications. The development of product specifications within a QbD framework should be aligned with global quality initiatives as defined in ICQ 8, 9, and 10. A risk-based approach should be used in the selection of CQAs, CPPs, and associated acceptance criteria.

Process Analytical Technology (PAT) creates a shift from traditional end-process testing to real-time, in-process testing and feed-forward/feed-backward control. PAT requires a change to an adaptive process that achieves a desired product target, as opposed to prespecified regulatory acceptance criteria. Implementing PAT will require a shift in thinking from both industry and regulators.

Workshop 1: What to Specify/Monitor?

Thomas Schreitmueller, Hoffman-La Roche presented "Selection of Critical Product Quality Attributes: A Case Study," followed by Christopher Holloway of ERA Consulting with "Action Limits and Their Application in the Context of Process Specifications – Case Studies." The presentations were followed by a discussion led by panel members Schreitmueller, Mark Schenerman, MedImmune; and Mats Welin of the Medical Products Agency. The discussion aimed to address the following questions:

1) Applications of Quality by Design in selecting critical product quality attributes:

a. How do we understand the correlations between clinical end point, critical product quality attributes, and critical process parameters?

b. Is the understanding of the physicochemical and biological/functional relevance of a given parameter sufficient to determine whether or not to control for that parameter?

c. How do we best understand and prioritize the key product quality attributes that merit direct control through specifications throughout the clinical development cycle?

2) Action Limits vs. Specifications:

a. What role should the desire to ensure manufacturing consistency play in the setting of specifications (i.e., is there value to setting specification for attributes that do not impact safety, efficacy, or stability)?

b. Is the use of action limits (especially in-process and less critical product quality attributes) a useful alternative to specifications for purposes of quality control?

What to Specify, What to Monitor?

Achieving more flexibility in the definition of an acceptable batch of a product is partly within the scope of Quality by Design. We are trying to extend or expand the design space beyond process robustness and also to implement critical quality attributes. Determining a critical product quality attribute can be reduced to a three-step procedure: discover the potential quality attribute, identify the relevant quality attribute, and control it.

Implementing a design space can begin with a unit operation rather than an entire process. Regulators need to have a high degree of assurance for the protection of human health and QbD submissions will have to include that degree of assurance. Therefore, sharing rationale and thought processes behind process decisions with regulators may be helpful.

It may be easier to maintain an existing specification rather than to undertake the time-consuming and expensive process of understanding what a particular parameter means for product efficacy and safety. It is becoming increasingly important to demonstrate to regulators the depth of your product and process understanding.

Quality by design won't necessarily replace the conventional approach. It may be an alternative approach for part or all of a process. It is not absolutely necessary to apply the quality by design paradigm to a whole process.

Historically, the drug industry has been wary of change. Part of the reason for that has been the difficulty of implementing new processes and procedures in such a highly regulated industry. It is important that regulatory agencies and drug companies work together for continuous improvement. Regulators have noted that relinquishing certain controls will require very good justifications. They need to be certain that your process can maintain an appropriate degree of assurance on the quality, and consequently efficacy and safety, of a product on an ongoing basis.

Quality by design is an iterative process that requires a huge amount of manufacturing experience and a thorough understanding of that experience. Therefore, we are likely to see only a relatively small proportion of sponsors actually being able to use prior knowledge effectively in a submission. A comment was made, for example, that a large number of the products seen in a centralized procedure are orphan drugs, where there is relatively little manufacturing experience. It would be unrealistic to apply the same paradigms to those as you do to a product that has been on the market for a decade and has a huge body of knowledge available.

There was the question of clinical trials and how to possibly address variability of a product. An ideal aim would be to build variability into clinical trials. However, the reality of clinically testing batch variability is probably impractical, due to the number of patients that would be required to obtain a statistically valid result. Some participants felt, however, that bringing clinical researchers into the design process would add value and result in more meaningful specifications.

There were questions and discussion on differentiating formal in-process controls from other in-process tests. When applying an in-process control, you must have a degree of confidence in the method applied to that control. A fully validated method may not be necessary; but at the very least, the method must have been demonstrated to be suitable for its purpose.

The question of biological function assays, or bioassays, was raised. Potency bioassays are used for routine control. The best models available for examining the biological function of a molecule can increase understanding of the product by an order of magnitude. A prerequisite for quality by design might be understanding not just the physicochemical, but also the biological properties of your product.

In any submission, regulators still have to be completely convinced that the sponsor has good control over and understanding of its manufacturing process. Traditionally, regulators have been provided with data. Supplying an agency with thought processes and justifications and less data is a relatively new concept. Companies can't come to regulators with esoteric

arguments; they have to provide real case studies. Industry needs to explain and share their thought processes and help to educate regulators about why their process is appropriate for this particular case.

That leads to the last conclusion, which is absolutely no surprise to any of us, that one size does not fit all.

Workshop 2: Release vs Shelf-life Specifications (One vs Two-tier Specifications)

Applications: A Case Study," by Karin Sewerin of Astra Zeneca; "Challenges in Setting Shelf Life Specifications for a Global Vaccine Product: Industry Perspectives" by Michel Duchene of GlaxoSmithKline; and "Setting Shelf Life Specifications: A Regulatory Perspective" by Philip Krause of CBER, FDA.

The panel discussion that followed included as panelists presenters Sewerin and Duchene along with Andrew Chang, PharmaNet Consulting; Earl Dye, Genentech, Inc.; and Kowid Ho, AFSSAPS. The discussion focused on the following questions:

1) What should be considered in setting shelf-life specifications?

a. Which factors should be considered in establishing shelf-life specifications (e.g., storage, handling, shipping, analytical variation, historical data)?

b. Are the shelf-life specifications limited to the release parameters that are indicative of protein degradation (e.g. proteolytic variants, aggregates, specific activity)?

c. How do the calculated values of release specifications influence shelf-life limit?

2) How do we best integrate setting of shelf-life specifications in clinical development and how they can be "adjusted" during life cycle of the product?

a. How should we consider the clinical study requirement?

3) What is a global acceptability of the two-tier specification concept?

Discussion Points and Summary Workshop 2

Exactly what do we mean when we say shelf-life specification? The real goal of setting any specification is to make sure that a product is going to have specific attributes, preferably relevant to clinical safety or efficacy, throughout its entire shelf life. Therefore, any specification that doesn't describe the product for its entire shelf is not technically a specification. The product must maintain its quality, safety, and efficacy for its entire shelf life.

The real issue, then, is how do we assure that the product maintains the necessary attributes — or meets specifications — throughout the duration of its shelf life?

The question was asked: What if you have a product for which the stability is known to be perfect? Any product is going to have some degradation profile. Even if the product is very stable, doubt remains. To make the claim that a product is stable, you need statistical information that tells you that it is stable and how certain you can be that it is stable. That requires more than doing individual tests at the beginning and the end of the dating period.

You must use a statistical analysis to define your level of confidence in that stability. That may depend on the variability of the assays you used to determine the potency, for instance, at the beginning and the end of the dating period.

So, what factors should be considered in establishing shelf-life specifications: storage, handling, shipping, analytical variation, historical data? The consensus was that all of these things should be considered. Historical data also is meant to encompass materials used in the clinic, because obviously the link to the clinic is very important in establishing any specification and especially one that is designed to assure product performance through an entire shelf life.

Are the shelf-life specifications limited to the release parameters or indicative of protein degradation? If you think about this question in the context of what we are trying to do, which is assure that the product is fit for use through its entire shelf life, the answer is clear. If we know, based on whatever data we have, that certain attributes could affect the stability, though they are not themselves stability indicating, those should be key things to which we pay particular attention in setting shelf-life specifications.

Then how do the calculated values of release specifications influence shelf life limit? We talked about different answers to that question. One is the so-called compliance model. The US FDA and other regulatory agencies offer guidance for setting both release specifications and shelf life specifications. Shelf life specifications must cover the stability, labeling, shipping, and handling of a drug product throughout its lifecycle. The goal of stability testing should be to reconfirm the degradation rate, not to test the quality of a single batch.

Another way of determining shelf life is using the general estimation method where you draw the regression line or try to predict what is going to happen over time and add in your error terms. It was pointed out that if you do multiple tests, and you want to make sure your product will be above your clinical limit on every one of those tests that in fact you have to set your release limits even higher. There are ways of making these calculations that are well understood.

We discussed the general applicability of the Arrhenius equation: When can it be used with confidence, and where is its applicability limited? There was a general feeling that it is useful in situations where interpolation within tightly controlled parameters is called for. There are reservations about its more general applicability, and caution would be needed in predicting actual shelf life from stress degradation studies. It was suggested that an alternative model, possibly the Williams-Davis-Landel equation, might be a better model.

Another very important point is the multiplicity problem. Not only is the manufacturer doing these tests, but also regulatory authorities all over the world. The more often you do one of these tests the greater your chances of a supposed failure, which can cause a serious problem. You have to figure out how to define the specifications for every one of those tests in a way that makes sense and doesn't put good product at undue risk.

How do we best integrate setting of shelf-life specifications in clinical development and how can they be adjusted during the life cycle of the product? There was general agreement that specifications need to be linked to clinical data. In some cases that link may be stronger, in

some cases weaker, but it certainly ought to always be explicitly considered. And the specifications need to be justified in the context of clinical information.

Adjustment of shelf-life specifications that are dependent on stability usually occurs when we have better stability data or revised stability estimates. Those can come from additional information obtained through annual stability programs, for instance. But it can also come as we gain increased confidence in those estimates. If we have more data the confidence intervals on those estimates may get smaller. That then may give us a better sense of what the specification ought to be. Or, as we improve our assays or we gain more information about the precision of our assays, those things can play a role in setting specifications and may also lead to a revision of a specification.

What is global acceptability of the two-tier specification concept? We have not really achieved consensus about what a two-tier specification is. The term *two-tier specification* implies that something is tested twice. And yet, for a product that is imperfectly stable, we are not in general taking every lot and comparing it with its expiry specification.

Do we call that a second tier? It's the clinical limit, but if we as a group call that clinical limit a specification, we are making an error. Because the term *specification* implies it is something every lot ought to be tested against. And that brings up a whole set of regulatory thinking and compliance thinking that doesn't serve the scientific discussion well at all. Some would argue against the use of the term *two-tier specification* because it implies something that we are not doing. There is general agreement that the purpose of all specifications, whether they are so-called shelf-life specifications, or two-tier specifications, is to make sure that the product has a certain level of clinical performance through its entire shelf life. Then the question is: how do you go about doing that?

There was a very robust discussion about some of the different ways of doing that. The vaccines model probably does have some applicability to some of the other therapeutic products. In any event it led to a very provocative and interesting discussion that may help move the goal posts here and make a difference in how we think about specifications and help us get around some of these very real problems that are caused by the way that specifications are currently applied.

Workshop 3: Setting Acceptance Criteria: Clinical Experience, Manufacturing Consistency, and Statistical Considerations

Presenters for Workshop Three included Martin Schiestl of Sandoz with "Justification of Product Specifications Outside the Clinical Experience;" Jorgen Iwersen of Novo Nordisk with "Setting Specification Based on Statistical Considerations;" Gerhard Koeller from Boehringer-Ingleheim, "Managing Specifications Through the Product Life Cycle: A Case Study of a Commercial Product;" and Marcus Dembowski from Roche Diagnostics presenting "Defining IEC Specifications as Parameters for Consistency or Purity."

The panel for discussion included the four presenters and Dieter Schmalzing, Genentech, Inc. Their focus was on the following questions:

1) Is it possible to justify specifications outside the clinical range?

a. How do we define clinical range/exposure: percentage of variants or total patient exposure on a mg/kg basis?

b. Are toxicology studies, in vitro studies, higher dosing in early clinical development appropriate alternatives?

c. Is the use of representative small-scale/development data relevant in setting specifications?

2) What are the statistical considerations (classical 3σ, tolerance intervals)?

a. What are the limitations of statistics in particular when a limited number of batches are available?

b. How best to capture both manufacturing and assay variability?

3) Life Cycle Management of Specifications (acceptance criteria)

a. Are interim specifications acceptable at the time of registration?

b. How often should they be revised? What is a relevant data set (number of runs, campaigns, sites, different sources of critical raw materials)?

c. What are the available mechanisms for changing specifications post-approval?

Discussion Points and Summary: Workshop 3

There was a brief discussion of what to do with analytical data that are not considered clinically relevant. We discussed as an example the intriguing question of glycoform distribution and a number of points were noted. You can't always conclude that glycoform distribution is clinically irrelevant. One opinion was that such information could with justification be regarded as process rather than batch control data. The regulatory viewpoint tended to disagree with that position, arguing that implementation as a consistency test has utility. Also, it was suggested that where such tests are carried out, though the limits might be wider than clinical experience would suggest you might still be able to avoid rejecting batches that might be perfectly suitable for use.

The first question asks is it possible to justify specifications outside the clinical range? A number of observations were made on the general subject of using clinical experience to set specifications and limits. These included the fact that you get different answers (with time) from regulators in different areas of the world. It was noted that such decisions must be related to the level of risk associated, and risk analysis is an inherent part of the process.

We discussed whether you should use application of absolute doses, such as mg/kg of impurities, rather than relative amounts, such as percentages. The former might have some clear scientific advantages, but present practical difficulties in application were noted.

There was a discussion on where useful clinical data might be obtained. It was generally recognized that all relevant clinical experience should be captured. The suggestion was made

for example of using post-phase 3 clinical extension studies. This was brought to the meeting's attention as something that might be of utility.

There was less agreement on the practical utility of deliberately widening clinical experience using materials that push the specification envelope. End-of-shelf-life materials or high aggregate were suggested as examples. It was felt that the latter approach should be undertaken only with considerable caution.

Industry members brought up the lack of clarity on the regulatory position. From the regulatory side, the response was that a one size fits all opinion is difficult to give because it doesn't exist. A specific example was posited to clarify the issue. The position of the regulators was sought. If a product had 5% XXX component and a clinical experience of three times stated dose, could you then apply a limit of 15%? Regulatory responded that a case by case risk analysis would be required.

Another question was the extent to which information can be transferred from one product to another. Host cell proteins were cited as an example where there might be some utility to such an approach. Other types of impurities such as aggregates would be much more product-specific. It was subsequently noted that even information from HCPs might be transferable only with caution because of potential variations in the nature of the proteins and in the assay methodology.

Generally it was agreed that setting specifications requires a long-term view of the product, from clinical trial data through to clinical accrued experience by end of product life — and as much of this long-term view as possible should be built into the front end design.

Moving to the second part of the session, statistical considerations, discussion addressed the central question of how experience gained from small scale with respect to batch number and clinical trials could be extrapolated to a manufacturing situation with a much larger number of batches. It was noted that the clinical uses of a product often change during its life, as variations in dose and regimen are adopted. Limits, of course, need to reflect such changes as they occur.

Finally, the third question addressed the issue of incorporating accrued experience into specifications during the product lifetime. Noted among a number of points was the uncertainty of estimates derived from both batch variation and assay variation. And the point was well made that the later component will inevitably decline as N becomes bigger as the number of batches is analyzed. We discussed possibilities for reducing the assay variability component earlier. The use of stability test assays for this purpose was recommended to the meeting.

We briefly discussed the use of interim specifications. At least one commentator suggested that while in theory the idea might be acceptable, it is not clear how this might be implemented in practice. The idea was endorsed in the panel.

And finally, in closing the whole discussion the point was again made that setting specifications is a long-term exercise rather than something that is done as a one-off on the basis of clinical experience. And the design implications of this should be recognized.

Workshop 4: Global Harmonization

The presentations for Workshop Four were "Managing Worldwide Specifications: Implications on Product Distribution" by Nadia Beaudoux, Eli Lilly and Company; and Anne Munk Jespersen, Novo Nordisk A/S presented "Harmonizing Specifications Globally, How Can It Be Done?". The two presenters were joined on the panel by Rohin Mhatre from Biogen Idec and Jasen Hampson with Amgen Europe. The discussion centered on the following questions:

1) What are the current challenges in compliance and product distribution with multiple specifications?

a. How can these challenges be overcome?

2) What is the relevance of multiple specifications to product safety and efficacy?

3) What opportunities are there for minimizing regional differences in specifications?

4) What is the role of pharmacopeias in setting specifications?

a. Can pharmacopeial processes help minimize regional differences in specifications?

DISCUSSION POINTS AND SUMARY: Workshop 4

Question 1 asked what are the current challenges in compliance and product distribution, and how can these challenges be overcome? Some proposals on how to overcome those challenges included looking into coordinated reviews and looking into mutual recognition. Some members of the audience suggested opening an ICH discussion on certain topics, although there was some controversy on the role of ICH. We have agreed that there are a lot of regulatory hurdles when developing a drug for a worldwide market, which are often difficult to overcome.

In terms of differences of specifications, the importance of flexibility regarding timing of implementation was considered very important. Regarding the discussion on monographs in pharmacopeia, there was not a full agreement on whether these monographs are useful. But it was agreed that in terms of harmonization we should put in some effort because in certain areas it can be of value. However, we need to take some criteria into account – for example, complexity of the products. The process is the product paradigm is still a valid element to take into account.

The issue of clinical relevance is still an important one to consider. We have been discussing the possibility of implementing quality by design. There are still some elements that we need to consider – for example, different processes for one product; the possibility of manufacturing in different regions. This type of thing will trigger reactions from regulatory authorities regarding specifications. So how do we address this – because processes evolve over time.

One question regarding ICH brought up an important element that we should think about – maybe not from a content perspective, but in terms of process, in terms of agreement. The regulatory aspect of ICH is still a difficult thing to consider. If we want to move forward we

should go ahead with these sorts of ideas and maintain communication with the ICH stakeholders. We talked a little about the idea of one global authority. It was also suggested that stakeholders engage the WHO in potentially filling such a role.

In conclusion, we need to take this information back to the different regulatory authorities, both our US colleagues and those of us working in Europe. We should try to multiply this type of event.

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Opening Plenary Session
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Workshop I: What to Specify/Monitor?
Session Chairs: Ilona Reischl, AGES PharmMed and Christopher Holloway, ERA Consulting

Workshop II: Release vs Shelf-life Specifications (One vs Two-tier Specifications)
Session Chairs: Philip Krause, CBER, FDA and Brigitte Brake, BfArM

Workshop III: Setting Acceptance Criteria: Clinical Experience, Manufacturing Consistency, and Statistical Considerations
Session Chairs: Wassim Nashabeh, Genentech, Inc. and Adrian Bristow, NIBSC

Workshop IV: Global Harmonization
Session Chairs: Jacques Mascaro, F. Hoffmann-La Roche, Ltd. and Ken Seamon, Institute of Biotechnology, University of Cambridge

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