US FDA Perspective: Recent Trends in the Regulation of Biopharmaceuticals

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Disclaimer

The views and opinions expressed should not be used in place of regulations, published FDA guidances, or discussions with the Agency.
Outline

• Advancement of biopharmaceutical industry
• Advances in lifecycle management
• Comparability/change protocols
• Biosimilar and breakthrough designation products
Development of Monoclonal Antibody Products

- Orthoclone (1st mAb)
- Rituxan
- Zenapax
- ReoPro
- Enbrel
- Mylotarg
- Zevalin
- Humira
- Vectibix
- Cimzia
- Adcetris
- Gazyva
- Nov 2016
- Blincyto
- Inflectra
- Biosimilar
- Vectibix
- QbD/design space
- raxibacumab
- Pegylated
- mAb-drug
- Conjugate
- BLA
- Human/mouse
- Human/phage display
- Therapeutic
- radioimmunoconjugate
- Intact chimeric
- humanized
- mAb-drug Conjugate
- NDA
- Fc-fusion
- Chimeric fragment
- Murine
- Adadapt from M. Shapiro, 2013
- 73 antibody products
- Nov 2016
Advancement of Antibody Products

Advancements in knowledge and understanding

- **Product**
  - Structure & Modification
  - Structure/Function
  - Stability/Formulation

- **Process**
  - Scale-up
  - Platform/Platform-like

- **Technology**
  - Manufacturing
  - Analytical
Changing Landscape of Lifecycle Management/Control Strategies
(including established conditions)

• Not ready for a 180° change in control strategies- However, ARE discussing and approving some advancements, including
  – Modification of control strategies for legacy products
  – Changing expectations for strategies at the time of initial BLA/PAS approval (not changing expectation of assurance of quality)

• Use of Multi-Attribute Methodology, Continued Process Verification, Predictive Modeling... as part of control strategies?

• Data and other information/evaluation to fully support proposed control strategies are required.
Example 1: Specifications – Part 1

Justifications provided:

• “Fragmented variants are well controlled by the manufacturing process, the historical level is consistently low, and minimal changes are observed on stability [under recommended conditions]. Therefore, rCE-SDS is not included for drug substance lot release or stability testing.”

• “Historical ... data is consistently low, the level of partial molecules is well-controlled during the manufacturing process with no practically significant changes observed over shelf life at recommended storage conditions. Therefore nrCE-SDS is not included for drug product lot release or stability testing.”

• “Fragmented variants [rCE-SDS] are monitored as an in-process control at the ... pool”

• “nrCE-SDS is monitored as an in-process control during drug substance manufacturing”
Example 1: Specifications – Part 2

Some questions/potential issues:

• Well controlled by the manufacturing process
  – How variable was the actual manufacturing process during clinical, development, engineering, and validation runs? How variable will the process be allowed to be post-licensure?
  – Minimal development data only for production bioreactor (and impact was identified), specific holds at harvest (and impact was identified), and low pH viral inactivation (and impact was identified) and only specific tests for specific steps. No data looking specifically at clearance.
  – No hold data provided and holds only evaluated using rCE-SDS.

• Historical level is consistently low
  – Historical versus future? Why are we examining DS/DP at release and on stability?
Example 1: Specifications – Part 2, cnt.

Some questions/potential issues:

- No practically significant changes observed over shelf life at recommended storage conditions
  - “Practically significant”?  
  - Historical versus future?

- “Fragmented variants [rCE-SDS] are monitored as an in-process control at the ... pool”
  - “Action limit” versus specification acceptance criterion (or “rejection” limit)
  - At which step does in-process testing make sense?

- “nrCE-SDS is monitored as an in-process control during drug substance manufacturing”
  - This in-process control is not included in 3.2.S.2.2 or 3.2.S.2.4.
    (Does the draft established conditions guidance say that having this control is a commitment and lead to a potential 483 observation/inspectional issue?)
Example 1: Specifications – Part 3

Potential justification to add:
The potential for this molecule to actually degrade via these pathways, given the forced degradation profile – if you stress a product many different ways and see limited degradation, is it logical to conclude that degradation through the pathways evaluated is sufficiently unlikely to occur in “real life,” even under worst case conditions?

• Thermal (super high temperature), accelerated/stressed temperature, high pH, low pH, ICH and other light stress, agitation...
  – 48°C (118°F) reduced = 3.7% fragment at 10 days
  – 40°C = 7.0% 3 months
  – 40°C non-reduced = 6.7% 3 months
  – ICH light = 4.3% 1.2 million lux hours
Example 2: Specifications

Justification (no reduced SDS assay):
• The LMW species will be controlled by SEC testing.

Key issue:
• The SEC method acceptance criteria include one specific LMW species, not any of the other species that have been identified, and it is not clear whether the detection of “new peaks” (relative to reference standard) is included in any aspect of the evaluation and would lead to an SEC assay failure.
Example 3: Specifications

Justification (SEC assay in-process only and not on stability):

• Testing for the in-process specification at the ... step [mid-purification] ensures aggregate levels are well controlled in the manufacturing process, as the ...step effectively removes aggregate species...

Questions/potential issues:

• Aggregate clearly impacts potency of this product as evaluated by one potency assay; however, the potency assay that is included as part of the specifications is not nearly as sensitive to aggregate.

• Other questions/issues similar to Example 1 regarding lack of data provided to support step at which in-process testing is performed (e.g., no data to demonstrate steps at which aggregate forms, including no hold data) and not including testing on the stability spec.
ICH Q12 Lifecycle Management

• “This guideline is intended to work with ICH Q8 to Q11 Guidelines and will provide a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle. Adoption of this guideline will promote innovation and continual improvement, and strengthen quality assurance and reliable supply of product, including proactive planning of supply chain adjustments. It will allow regulators (assessors and inspectors) to better understand, and have more confidence and trust in a firm’s Pharmaceutical Quality System (PQS) for management of post-approval CMC changes.”

• “Harmonised approach to ‘regulatory commitments’”

• “Delineate the appropriate level of detail and information necessary for regulatory assessment and inspection in the dossier”

• “Introduce the concept of a post-approval management plan that can be used to proactively identify post-approval changes and the mechanism to submit and assess these changes by regulatory authorities (Assessors and Inspectors)”

• “Establish criteria for post-approval change management protocols that can be adopted by the ICH regions (enabling a harmonised proactive approach for lifecycle management)”

• “Encourage enhanced product development and control strategy approaches (Quality by Design (QbD)) providing opportunities for scientific and risk based foundations for post-approval change management plans”
Established Conditions

- The Guidance is intended to clarify what aspects of an application should be established conditions
- “The description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy, as defined in an application, that assure the process performance and quality of an approved product. Changes to the established conditions must be reported to FDA…”
- “…Sufficient detail should be provided in the application regarding the proposed established conditions to assure process performance and quality of the approved product.”
- Rationale: 21 CFR 600’s and 300’s
Established Conditions

• What they are:
  DS/DP manufacturing and testing facilities; source and specifications for starting materials for biological products; process, including in-process tests and sequence of operations, equipment, and process parameters and their ranges; specifications, etc.

• What they are not:
  Batch records (however manufacturing / control strategy changes may require updates that should be submitted); Development data; Characterization data; Validation data; Batch analysis data; etc.

• Where they are commonly located in the CTD
  “The relevant information would still be considered an established condition even if it is located in a CTD section not specified below [in the list that follows].”
Example 4

Noted on inspection:

• A DS unit operation that is typically completed in < 1 hour ran for ~16 hours.

• This was not considered a “deviation” or “event,” because a time limit for this step is not included in the description of the manufacturing process (i.e., 3.2.S.2.2).
  – The step is intended to run in a continuous manner. We also don’t want to require that every step/portion of a step have a time limit as part of ECs.
  – Why was a situation that was so atypical of the historical process not considered an event/deviation?

• As part of the investigation of the deviation for which the process was delayed, overall product quality was not evaluated.
  – That particular deviation was in regard to a protein concentration result, and the investigation was only about the concentration result.
  – The investigation did not consider the impact of the “corrective actions” that were taking place (i.e., putting moving the material forward on hold until the concentration issue was resolved).
Example 4

• Responses to questions during the inspection:
  – Quality is okay, because the DS met specifications.
    • The proposed specifications were extremely limited with respect to purity.
    • Manufacturers are trying to use control of the process to support limited specifications. What should happen when the process does not run correctly?
  – The [unrelated] hold time at the end of the step is so short (relative to the 16 hour delay), because that validated time is related to microbiological concerns and that is the longest time we have at scale. The small scale pool hold quality data show much longer acceptable hold times.
    • The pool hold is performed under conditions that are different than what was basically a hold during the step, so there would have to be additional information to support the use of these data as part of an investigation.
    • No quality data were submitted to the BLA to support the hold times.

Established Conditions, “Enhanced” Control Strategy/Testing, Quality System, etc. – All aspects need to form a complete strategy that provides appropriate control to lead to a product of consistently high/correct quality.
Comparability/Change Protocols

• Can be used to manage changes to established conditions.

• Draft Guidance for Industry: Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information (April 2016)

• Have been used for product introduction to DS/DP manufacturing sites and additional manufacturing sites.

• Protocols are frequently approved for manufacture of new working cell banks and new reference materials/standards, resin and membrane reuse, and reprocessing.
Comparability/Change Protocols - Common issues:

• Lack of data to support analytical comparability acceptance criteria
• Analytical comparability acceptance criteria that are the same as release criteria
• Lack of mechanism for evaluating comparability of stability
• Requests for downgrade of subsequent submission(s) for changes that cannot be downgraded due to requirements in addition to analytical comparability, e.g., inspections
• CP (with or without requests for downgrade) for changes that would include requirements in addition to analytical comparability that do not address the additional requirements, e.g., validation
  – Information for validation (validation protocol) could (at least sometimes) be included in the CP
Biosimilar Products
(extensive CMC early in lifecycle)

• Advanced knowledge → reverse engineering, process development, CQA understanding and risk ranking, analytical techniques to examine

• To date (November 30)
  – FDA approved four 351(k) BLAs for biosimilar products, Zarxio (filgrastim-sndz), Inflectra (infliximab-dyyb), Erelzi (etanercept-szzs), and Amjetiva (adalimumab-atto).
  – There are 8 companies that publicly announced they submitted a total of 12 applications for biosimilar products.

• As of November 30, 2016, 66 programs were in the Biosimilar Product Development (BPD) program. CDER has received meeting requests to discuss the development of biosimilar products for 21 reference products.
Breakthrough Therapy Products
(expedited product development, sometimes more changes post-marketing)

• Advanced knowledge → Expedited CMC development, risk benefit evaluations

• BT designation is intended to expedite the development and review of drugs for serious or life-threatening conditions.

• BT designation does not change general CMC requirements and expectations.

• 10 of 45 novel drugs approved in 2015 were breakthrough – 5 were biotech products: asfotase alfa, daratumumab, elotuzumab, idarucizumab, and sebelipase alfa (joining blinatumomab, nivolumab, obinutuzumab, pembrolizumab)
Expectations for Quality

Patients and caregivers assume that their drugs:
- Are safe
- Are efficacious
- Have the correct identity
- Deliver the same performance as described in the label
- Perform consistently over their shelf life
- Are made in a manner that ensures quality
- Will be available when needed

FDA considers these aspects when evaluating lifecycle management plans and control strategies.

Adapted from Susan Kirshner – CMC Strategy Forum Japan 2015
Conclusions

We look forward to discussions regarding new strategies for lifecycle management and change reporting and the development of new products with challenging CMC aspects.
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