Breakout Session A

Physical Chemical Characterization and Impurities

FDA/DIA Scientific Workshop on Follow-on Protein Pharmaceuticals

Moderators

FDA:	Barry Cherney Andrew Chang Stephen Moore
Barr Laboratories:	Charles DiLiberti
Genentech:	Reed Harris

Question 1

- Which product attributes should be evaluated?

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Reed Harris:

- What is known about molecular characteristics that mediate:
    * Bioavailability
    * Potency
    * Safety (including immunogenicity)
- What is known about the routes of degradation:
    * Effects of container and/or storage conditions
- Process-related impurities:
    * Host cell proteins, leachable compounds

Which product attributes should be evaluated?

Charles E. DiLiberti:

- Perform full physical/chemical characterization using all available and relevant comparative analytical tools
- Perform redundant measurements of each aspect of structure and purity with multiple orthogonal methods
- Address identity, purity, and potency
- Analytical results collectively provide highly sensitive and selective fingerprint of product

Which product attributes should be evaluated?

Audience / moderator comments:

- All relevant parameters should be evaluated
  - No need to test to infinity
  - Historical data base needed
  - Value of literature
  - Based on sound science and product class (e.g., bacterial expression systems don’t need glycosylation data)

Which product attributes should be evaluated (Cont.)?

- Perceived clinical issues: safety, efficacy
  - All properties may be relevant for safety
- Discussion regarding what *relevant* means
- Orthogonal approach needed
  - May not find what you're not looking for

Question 2

What are the capabilities and limitations

of the available analytical tools to evaluate

those identified product attributes?

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Reed Harris:

- Limits: *ƒ* (length) (# modifications) (# polypeptides)
- Single modification type at multiple sites
  vs. variable modification at one site
- Higher order structure methods
- Examples: deamidation and aspartate isomerization
- Glycosylation (N-linked, O-linked, site occupancy, terminal groups)

What are the capabilities and limitations of the available analytical tools to evaluate those identified product attributes?

Charles E. DiLiberti:

- Complete comparative characterization is both possible and routine for most protein products, and provides the foundation for supporting product changes and comparisons
- Similar logic and criteria should be used for comparisons between products from different manufacturers
- Complete elucidation of covalent structure
- Sensitive methods for comparing higher order structure (fingerprint)
- Sensitive methods for measuring impurities

What are the capabilities and limitations of the available analytical tools to evaluate those identified product attributes?

Audience / moderator comments:

- Discussion centered on *limitations*
  - ability to detect clinically relevant properties
  - “absolute” vs. “comparative” characterization
  - mechanism for Eprex immunogenicity
  - hGH process change (immunogenicity)
  - Comparing HCPs from one manufacturer to another (HCPs meant to monitor process, not safety)
  - acidic forms of MAbs
  - succinimide forms
  - aggregates (literature re. effects on biological activity)
  - glycosylation
  - leachates
  - aspartate isomerization (isoAsp has same charge and mass)

What are the capabilities and limitations of the available analytical tools to evaluate those identified product attributes (Cont.)?

- Challenge of comparing quantitative results across independent labs (e.g., hGH strength)
- Capable of generating ample data
  - how to use the data (e.g., glycosylation: site occupancy, terminal glycans, fucosylation)
- Physicochemical methods have improved significantly
  - still not absolute - limitations remain, extent is subject to opinion
  - limitations can trigger additional studies (PK, PK/PD, clinical)
- Follow-On manufacturer:
  - might use better methods than the innovator
  - not privy to current innovator methods
- Innovator may continue to find new characteristics over time

Question 3

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Reed Harris:

- How to apply “comparability” concepts without a historical data set?
- How to link FOPP lots to the innovator’s clinical material without a common reference, methods, or reagents?
- To what extent does a FOPP manufacturer re-characterize, assign impurities etc.?
- How to determine that FOPP is monitoring critical quality attributes?

What are the appropriate standard(s) for the comparison of those identified product attributes?

Charles E. DiLiberti:

- In most cases, the brand product is the appropriate comparator.
- Acceptance criteria should be based, in part, on brand product variation.

What are the appropriate standard(s) for the comparison of those identified product attributes?

Audience / moderator comments:

- Drug product as comparator
  - this is the product that goes into people

- Excipients may interfere with analysis of API
  - extraction may affect API characteristics
  - may be able to validate methods by adding/removing excipients

- May need to evaluate intermediates and bulk drug substance in addition to the drug product

What are the appropriate standard(s) for the comparison of those identified product attributes?

- Pharmacy samples :
  - number of drug product lots needed for analysis by FOPP (e.g., may depend on complexity and purity of product)
  - may compare to multiple innovators
  - FOPP mfr does not know how many API batches are represented
  - impact of stability (not working with fresh material)
- Reliance solely on limited sample set may lead to specifications that are tighter than innovator's
  - ability of product reviewer to decide on FOPP specs without reference to innovator's proprietary information
- FOPP specifications based on innovator's clinical experience via analysis of marketed lots

Additional Comments

- Comparability within a manufacturer vs. follow-on
  - in-process materials, historical data, clinical experience not available to FOPP
  - extent of manufacturing changes (incremental vs. *de novo*)
  - reference standards, monographs available for some products

- Control process to limit modifications (i.e., heterogeneity)

- Innovators may stop sharing their experiences if their disclosures are used to support FOPP applications
  - industry standards may be harder to identify

- Industry thanked for sharing their experiences where something went wrong - this could help all manufacturers avoid repeating the same mistakes