Experience in comparability exercise in US

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Demonstrating Product Comparability and Impact on Product Approval and Supply for Protein Therapeutics

- Characteristics of Protein Therapeutic Drugs
- Comparability Protocol
- Impact on Enbrel®
  1. Initial Approval
  2. Post approval changes
- Factors for Success
- Challenges and Opportunities

Characteristics of Protein Therapeutic Drugs:

Characteristics of Therapeutic Proteins

- Obvious
  - Products are heterogeneous and three dimensional structure is still difficult to determine routinely
  - Process is linked to a biological production system which is less defined than chemical synthesis
  - There exist specific concerns with aseptic integrity and adventitious agents
- Not so apparent
  - Products can be characterized using numerous sensitive and discriminating techniques
  - Process can be controlled and characterized
  - Product is frequently quite robust with regard to process changes

Charactetistics of Protein Therapeutic Drugs:

Example of Product Quality Control

Step	*Control Points*
Fermentation	111
Purification/Formulation	80
Drug Substance	16
Drug Product	19

- Process Monitoring and Controls
  - Data points include product and intermediate data as well as process data: Not all are critical control points!
  - Critical control points are identified through process characterization and validation
  - This number of control points does not include the many environmental/facility or raw material testing controls

Comparability Protocol:

Role of Comparability

- ***One of the most important operational concepts for fostering cost effective development and commercialization***
- Licensing provisions of PHS Act and CBER policy restricted implementation of manufacturing changes and resulted in clinical testing after significant changes in manufacturing
  - Scale up, site changes, process changes
- Industry said:
  - *"We need flexibility that allows analytical methodologies to support comparability without complete clinical evaluation."*
- FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products, April 1996

Comparability Protocol:

Definition of Comparability Protocol

- Precedent with Stability Protocol
  - Defined set of tests for assessing stability
  - Allows dating to be extended using Annual Report based on approved Stability Protocol
- A well defined, detailed, written plan for assessing the effect of specific CMC changes in the identity, strength, quality, purity, and potency of a specific drug product as these factors relate to the safety and effectiveness of the product

A comparability protocol describes the changes that are covered under the protocol and specifies the tests and studies that will be performed, including the analytical procedures that will be used and acceptance criteria that will be achieved to demonstrate that the specified CMC changes do not adversely affect the product.

Comparability Protocol:

Benefits of Comparability Protocol

- Reduction in Reporting Category from PAS (4 month) to CBE(30)
  - Significant impact on managing product supply
- Agreement with FDA on data requirements and criteria
  - Eliminates “regulatory risk” with regard to requirements for approval
  - Places burden on Industry to meet data requirements
  - Facilitates review by FDA staff
  - Benefit is realized even in the absence of reduction in Reporting Category

Comparability Protocol:

Successful Comparability Strategies

- Strong development data
  - Defined change
  - Validated small scale models
  - Supportive stability data (if necessary)
- Sensitive analytical methods
  - Defined acceptance criteria
- Manufacturing history
  - clinical or commercial
- Validation strategy
  - Equipment qualification
  - Process validation

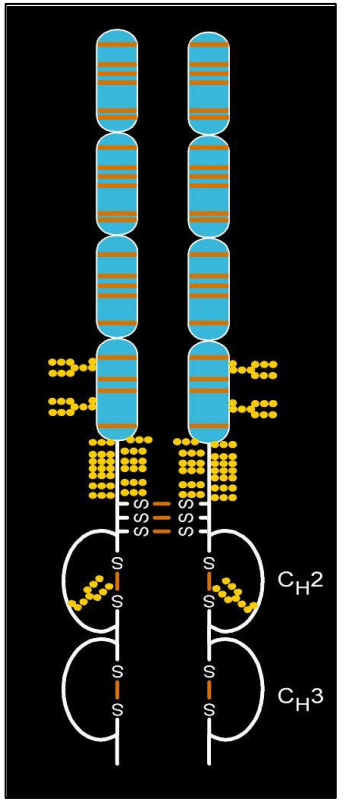
Comparability Protocol:

Content of Comparability Protocol

- Background
- Process Development Overview
- Comparability
  - Analytical method comparability
    - Release tests
    - Characterization tests
  - Stability
  - Process Comparison
  - Acceptance Criteria
- Bioequivalence (as needed)
- Attachments
  - Detailed process information
  - Detailed statistical information on manufacturing release data

Impact of Comparability on Approval of Enbrel® - TNFR:Fc

- First biologic therapy approved for rheumatoid arthritis (RA) and juvenile RA
- Unanticipated market acceptance
- Successful clinical trials in Rheumatoid Arthritis drove need for scale-up of the Enbrel® process
- Process scaled-up to 12,500L at Boehringer Ingelheim Pharma KG (BIP) for commercial production
- Data demonstrating comparability between the 1600L and 12,500L scales was submitted as part of the BLA filing for Enbrel®



Enbrel: Impact of Comparability Protocols

- Regulatory Approvals
  - Initial Product Approval with Scale Up
    - Phase III trials at 2000L pilot scale
    - Commercial scale at 15,000L supported by analytical data and pk equivalence
  - 1st Process change at first commercial site supported by analytical data using comparability protocol approved as a CBE30
  - 2nd Process change at first commercial site with analytical data using comparability protocol approved as a CBE30
  - Second commercial bulk and fill site supported with analytical data and approved as a PAS within 4-month review
- ***Yes: current FDA policy and regulations provide great opportunity for manufacturers of biotechnology products***

Initial Approval:

Process Transfer from Immunex to BIP

- Provided a linkage between the clinical stage process and product and the process and product made at the commercial scale.

- Testing included comparison of:
  - cell culture process parameters
  - purification process parameters
  - biochemical characterization
  - animal PK studies
  - human PK studies

Initial Approval:

Analytic Methods for Comparability

- Size exclusion chromatography
- Peptide map
- IEF gel
- Oligosaccharide profile
- Sialic acid analysis
- Monosaccharide compositional analysis
- Bioactivity and binding activity
- SDS-PAGE-Coomassie and silver stain
- N-terminal sequencing
- C-terminal sequencing
- AAA
- Process related impurities

Initial Approval:

Pharmacokinetic Comparability

- PK studies performed in a murine and non-human primate model
- Human bioequivalence study also conducted
- PK parameters evaluated and found to be comparable

Initial Approval:

Enbrel Approval

- Comparability was demonstrated between Enbrel® manufactured at Immunex (1600L) and BIP (12,500L)
- The testing plan was multifaceted and included comparisons of cell culture and purification process parameters, biochemical characterization, and animal and human PK studies
- Commercial manufacturing history since completion of the comparability study supports the use of this strategy for introducing process changes.

Post Approval Changes:

Reduction of Reporting Category from PAS to CBE30

- Key drivers for changes
  - Enhance product quality
  - Enhance process robustness
  - Improve process yield
- Process Changes
  - Upstream conditions and media
  - Growth conditions and cell parameters
  - Downstream column geometry
  - Additional column steps
- Regulatory Pathway
  - Utilization of Comparability Protocols
  - Analytical data submitted
  - Approved using CBE30

Post Approval Changes:

Approach for Comparability

- Used the previously described 1600L scale model to simultaneously test and introduce multiple process changes
  - Small-scale development at one and 80L scale
- Extensive pilot scale development data to demonstrate process performance and analytical comparability to commercial process.
  - For development used the 1600L pilot-scale process previously demonstrated to be a good model for the commercial scale Enbrel® process
  - Process and product comparison of several 1600L development lots to commercial Enbrel® process and product data
- Analytical comparison of three conformance BDS lots with commercial product manufactured at the same site

Post Approval Changes:

Analytical Approach for Comparability

- DS release tests
- DP release tests
- Additional characterization tests
  - Identity-Western blot
  - Charge heterogeneity - IEF
  - Primary, secondary, tertiary structure: AAA, far and near UV, differential scanning calorimetry
  - Purity - SDS PAGE (silver) and denaturing SEC
  - Negative charge heterogeneity - AEX
  - Carbohydrate composition
- 1:1 Co-mix tests
- Select in-process tests

Post Approval Changes:

Approval of Process Changes

- Extensive groundwork at the pilot scale to demonstrate process robustness and analytical comparability to the commercial product
- Approach with conformance lots focused primarily on analytical comparability
- Enbrel® produced in the conformance runs using the modified process was shown to be comparable to commercial Enbrel® .

Post Approval Changes:

Approval of New Facility

- New DS and DP Facility
  - Same Process
  - Process equipment modified to accommodate facility
- Comparability protocol reviewed
  - DS and DP analytical data
  - Process comparability
  - Stability requirement
  - Data compared to current manufacturing history
  - Validation data reviewed as part of PAI
- No Impact on Reporting Category
  - Review significantly facilitated by agreement on requirements to establish comparability
- 4-month review and approval achieved

Factors for Success:

Success Factors and Challenges

- Regulatory Success
  - Well documented process and development history
  - Comprehensive product characterization
  - Good small scale models for commercial scale process
  - Well thought out strategy for development and commercialization
  - Open partnership with regulatory reviewers
    - Early discussions on strategy
    - Frequent updates on status, data, and changes to plan

Challenges and Opportunities:

FDA Guidance on Comparability Protocols

- Comparability Protocols - Chemistry, Manufacturing, and Controls Information, Feb 2003
  - Applicable to NDAs, ANDAs, NADAs, ANADAs, synthetic peptides
  - Not applicable to proteins or BLAs
- Generally consistent with current experience
- Main benefit is reduction in reporting category
  - Acknowledges the use of protocols even when they do not result in changes in reporting categories
- Specifies detailed information on specific change and test
  - Limits potential to develop a multiple use protocol

Challenges and Opportunities:

Comparability Protocols - Issues

- Timeframe for Changes (~1-2 years)
  - 4-month review of protocol as a PAS
  - Equipment Qualification (IQ/OQ/validation)
  - Lot testing
  - Submission
- Multiple Use of Protocols
  - Changes in downstream steps such as columns
  - Changes in fermentation parameters
  - Changes in scale
- Enhancing the use of protocols
  - Accelerated review
  - Review of protocols even if they do not result in changes in reporting category

Challenges and Opportunities:

Standards for Approval - Issues

- Drug Substance and Drug Product Data
  - Relatively straightforward to define
  - Some changes may result in differences in molecule that can be rationalized with regard to safety and efficacy
- Process Validation
  - Standards are less defined
  - Results in uncertainty with regard to GMP inspection
  - Validation standards:
    - Scientifically based
    - Reflect current manufacturing state of the art and reflect operations

Challenges and Opportunities:

Status of Comparability and Process Changes

- Technical
  - It is possible but challenging to make changes to sites and processes.
  - Robust processes and manufacturing history are key elements to success.
- US Regulatory
  - Regulatory pathways are straightforward
  - Comparability is still not generic and needs to be defined for each product or process change, however using a successful template can be very helpful
- Global
  - Complicated due to different requirements and review times
  - It is not clear that ICH can address all of these issues