Developing International Regulatory Standards for Biosimilars

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The Importance of Data Over Time

- 2003: FDA approved innovator Wellbutrin 300 XL
- 2006: Generic Budepropion XL 300 approved
- 2007: 85 AERs reported for loss of antidepressant effect with generic drug
- 2008: FDA reviewed a six-month bioequivalence study on Budeprion XL 150 and found no basis for AERs
- 2010-2012 Additional AERs reported, FDA initiated new bioequivalence study, which demonstrated lack of bioequivalance among multiple generic versions.
- 2013: Teva and Watson withdrew their products from the market at FDA's request, *Six years* after AERs initially received
- **The lesson: it is important to get good data over time before approval, as problems can emerge over time and it can hard to get a medicine removed once approved.**

Equivalence/interchangeability

- Problematic with some drugs
- Potentially dangerous with biologics
- Complexity of biologics and sensitivity to manufacturing differences suggest a strong need to track and trace effectively.

Generic Drug Equivalence

- Same
  - API
  - labeled strength
  - dosage form
  - route of administration
  - Labeling
- Therapeutically equivalent (fully interchangeable) with reference product

Generic Drug Equivalence

vs.

Biologic Comparability

- Straightforward process
- Demonstrate chemically identical
- Identical detection in bloodstream

- A comprehensive comparison
- Many analytical measurements
- Many interactions must be analyzed.

Generic Drug Equivalence

- **A straightforward process:**
- 'Similar' bioequivalence
  - 80 – 125% of brand name
  - Often demonstrated by bioavailability
  - May not be required for all dosages/dosage forms
- Does not mean equivalent formulations
  - Differences in amount, type of excipients
- Does not mean all dosages have been demonstrated to be bioequivalent
  - Bracketing approach, risk assessments

Comparability Exercise

- ICH Q5E - Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (2004) **requires comprehensive comparison**

- ***May*** include:
  - Physicochemical properties
  - Biological activities
  - Immunochemical properties
  - Purity, Impurities and Contaminants
  - Product and test method specifications
  - Stability
  - Comparison with process validation batches
  - Comparison with batches used in clinical trials
  - May require additional clinical and/or non-clinical data

Comparability is Not a GPS

- Q5E does not provide a road map
- There is no precise formula for biologics, as with chemical drugs
- Demonstrating comparability of an innovator product before and after manufacturing changes is NOT the same as demonstrating comparability between two different products, e.g., innovator and biosimilar

Challenges of Biologic/Biotech Drugs

- May be sourced from biological materials
- Often grown, not compounded- 'the process is the product'
- Often subject to aseptic manufacturing requirements
- Additional biologics regulations (21CFR 600 -680) require product licensing, additional standards, lot release, etc.
- Slight differences can have substantial effects on final product:
  - Amino acid sequence differences
    - Same protein, same immunogenicity, different biological activity
  - DNA methylation patterns can vary depending on host cells
    - Alters gene transcription
  - Post-translational modification of proteins
    - Glycosylation, phosphorylation, e.g.
    - Affects/determines biological activity

Meeting the Challenges of Biologics

- The Complexity and sensitivity of biologics pose an extra level of challenges
- FDA is up to the task, it is wisely pursuing a cautious approach
- The extra need for pharmacovigilance with biologics must be a priority globally
- There are currently several different regulatory systems, international standards would be helpful.

Current situation

- Borderless industry
  - International supply chains
    - Difficult to track
    - Not always possible to identify original source/manufacturer
  - Multi-country manufacturing is very common
- Regulatory systems are localized to individual countries
  - Inconsistent, overlapping regulations
  - Highly variable enforcement strategies

Building an International Framework

- In a global marketplace, it is important to create an international system with robust standard setting.
- What data are required to show safety, efficacy, comparability? Over how much time?
- Problems of setting biologic standards need to be solved now, before the proliferation of many different systems.
- Several organizations are working cooperatively to develop such standards.

International Efforts

- Increased cooperation between national regulatory agencies (FDA, EMA, MHRA, TGA, MOH, etc.)
- ICH – International Conference of Technical Requirements for Registration of Pharmaceuticals for Human Use
- PIC/S – Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
- WHO – World Health Organization

ICH

- Harmonized guidance documents on a wide variety of quality, safety, efficacy and multi-disciplinary topics
- Q7A, e.g, has helped to establish a solid platform of API manufacturing standards world-wide
- Documents are applicable as guidance in most countries
- Have force and effect of law in only a few (e.g., Europe)

PIC/S

- Another tool
- Standardization of inspectional efforts world-wide
- Train pharmaceutical inspectors
- Assess inspectorates
- Guidance documents

WHO

- Disease surveillance
- Guidance documents
- Designate INNs
- Wide variety of other programs

Steps forward

- International regulatory system
  - Consistent body of regulations
  - Consistent application of regulations (product reviews, inspections, etc.) worldwide
  - Sufficient enforcement power to make them stick
- Great idea, not a quick and easy project

Steps forward

- Establish US Biosimilar regs that
  - Recognize the uniqueness of biologics
  - Can be implemented and enforced by FDA
  - Learn from the known problems with generic drugs
  - Build upon EMA's experience
  - Serve as a model for other countries

Steps forward

- Establish Biosimilar naming convention
  - Simple
  - Logical
  - Provides quick recognition of product
  - WHO has led the way in this regard.
- Education of patients, physicians, regulators is key

Thanks for your attention

Biological Drugs

- *Biological product* means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man - 21CFR 600.3