Pharmacovigilance for biotherapeutics: Partnering for patient safety

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Types of pharmaceutical products

• *Chemically-synthesized small molecule medicines*
  – Made by chemical synthesis
  – Small, simple, low molecular weight
  – Easy to characterize and purify
  – Rigid and stable in structure

Example shown: Valium
Types of pharmaceutical products

• Biotherapeutic medicines
  – Biological synthesis using human DNA segments, bacterial or animal cell lines
  – Large, heterogeneous, high molecular weight
  – Flexible, labile structure
  – Difficult to characterize and purify
  – Complex manufacturing process
# Types of pharmaceutical products

<table>
<thead>
<tr>
<th>Chemically-synthesized Small Molecule Medicines</th>
<th>Biotherapeutic Medicines</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Produced through a step-by-step chemical synthesis process</td>
<td>✓ Produced with a biological synthesis process and derived from proteins and other substances produced by living organisms</td>
</tr>
<tr>
<td>✓ Characterized by small molecule composition</td>
<td>✓ Composed by large and complex molecules which are difficult to characterize</td>
</tr>
<tr>
<td>✓ Relatively simple organic compounds containing few functional molecular groups</td>
<td>✓ More sensitive to change and the end product is determined by a wide range of factors, including the manufacturing process</td>
</tr>
<tr>
<td>✓ Typically prescribed by a primary care physician and self-administered at home</td>
<td>✓ Generally used for the treatment of severe diseases and therefore mostly administered in hospitals with the assistance of medical personnel (with exceptions such as self-administered insulin)</td>
</tr>
</tbody>
</table>
## Types of pharmaceutical products

<table>
<thead>
<tr>
<th>Small molecule drug</th>
<th>Large molecule drug</th>
<th>Large biologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin 21 atoms</td>
<td>Human growth hormone (hGH) ~ 3,000 atoms</td>
<td>IgG antibody ~ 25,000 atoms</td>
</tr>
<tr>
<td>Bike ~ 20 lbs</td>
<td>Car ~ 3,000 lbs</td>
<td>Business jet ~ 25,000 lbs (without fuel)</td>
</tr>
</tbody>
</table>
Monoclonal Antibody

Adapted from Steven Kozlowski, Director OBP, FDA

Aspirin
Protein Microheterogeneity

Small Molecule Drug

Protein Drug
Biotherapeutics’ characteristics underscore the importance of pharmacovigilance

- A complex production process
  - Intrinsic variability
- A potential for generating unwanted immune responses
  - Potential for delayed onset adverse reactions

Importance of specific traceability
Understanding benefit-risk

Benefit/Risk Management Plans

More Defined

Optimize Individualized Population

Uncertain

Phase 3 Trial Population

Label Population

Off-label & Noncompliant Population

How to Best Manage This Transition?

Personalized Health Care (biomarker, Bioimaging, ...)

Lack of external validity

Lack of communication

Efficacy-Effectiveness Gap
New key Stakeholders have emerged
Full transparency expected by «Society»
Stakeholders / Communication

- Patient
- Prescriber
- Marketing Authorization Holder
- Regulators
Pharmacovigilance is a key pillar in the concept of biosimilarity
Current situation for SBP naming

Japan
- Adopted distinct non-proprietary naming using INN as base
- Example: INN – follow on 1 INN – follow on 2

Australia
- Generally follows EU system of approval for naming
- Made exception for epoetin SBP – gave distinct name
- Naming policy currently under discussion

US
- USAN Council works closely with WHO to harmonize names for substances
- Draft biosimilar guidelines require differentiation
- Naming policy currently under discussion

Canada
- No specific policy on naming for SBPs
- Naming policy currently under discussion

Brazil
- No specific policy on naming for SBPs
- Naming policy currently under discussion

EU
- Uses INN system, but recommends Trade Name be used in addition to distinguish among biotherapeutic products
- Indicates WHO INN system will remain established system in EU

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The INN system

• INN plays a central role in:
  – National pharmacovigilance and traceability systems
  – National systems for substituting medicines

• Limited control over use of existing INNs
  – Applicant decides if new INN wanted/required
  – If existing INN is chosen, National Regulators are accountable

• Under current WHO criteria, possible for multiple biologics to have the same INN with different clinical characteristics

• As a result: no clear INN differentiation between similar products
The role of INN in pharmacovigilance needs to be further considered

- WHO should determine on a global level how current naming system can be applied to retain INN goals – clear identification, safe prescription and dispensing
- WHO INN Committee and WHO Pharmacovigilance Committee work together to develop global recommendations for an effective mechanism for tracking and tracing biotherapeutic products
  - Prevents weakening of INN system
  - Provides uniform international standard for biotherapeutics
  - Facilitates linkage of an adverse event with the appropriate product
  - Promotes communication and exchange of information among health professionals and scientists worldwide
New Legal Requirements in the EU

Article 102 of the Medicinal Products Directive 2011/83/EU, as amended by Directive 2010/84/EU, deals with the identification of medicinal products when reporting adverse events. Article 102(e) provides clarification specifically for biological medicinal products.

The Member States shall:

(e) Ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number [Emphasis added].
New EU Pharmacovigilance Legislation*

EU Objectives:
- Strengthen post-authorization regulation of medicines
- Improve efficiency within the industry
- Reduce duplication of Member State efforts
- Increase transparency

Opportunities:
- Improve patient safety
- Maintain compliance by meeting the new EU PV Legislation
- Adapting to new treatment developments and innovative therapies

→ Compliance by all stakeholders is therefore of utmost importance!

Conclusions

• Biotherapeutic medicines are complex products with specific safety issues compared to chemically-synthesized small molecule medicines

• Identification and traceability are essential for pharmacovigilance processes
  – Reporting brand name
  – Batch number

• All stakeholders have a role in ensuring robust pharmacovigilance for biotherapeutics
THANK YOU!

Tänan
Merci
Shukriya
Dōmo Arigatō
谢谢