



Interchangeability: What is Next?

Analysis of the concept & of the FDA Draft Guidance

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Leading on Biosimilars: The 2017 AAM Biosimilars Council Conference
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Outline

- Concept of Interchangeability
 - Terminology
 - Legal basis for interchangeability
 - State substitution laws
 - Purple Book

- Review and analysis of FDA Draft Guidance
 - Clinical study design
 - Endpoints
 - Reference product
 - Extrapolation
 - Post-marketing safety data
 - Comparative and quantitative human factor studies of the drug device

Terminology can be confusing

- Terms “interchangeability” and “substitution” are used differently in the US and Europe
 - Additional related terms: “Switching” and “Transition”
- There are two situations that need to be considered irrespective of terminology

Situation #1: Physician initiated

1. When a **physician** writes a prescription for a biosimilar as a refill for a patient that previously was treated with an originator
 - Transition: FDA term for a single switch from reference product to biosimilar
 - Switching: (EU legal definition) “Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment”

Physician always has the ability to prescribe whatever therapy she/he believes is appropriate for a given patient in a given situation

<http://www.biosimilarsforum.org/biosimilars-insights/biosimilars-faqs> (accessed Sept 5, 2017)

European consensus Information Paper 2013. What you need to know about Biosimilar Medicinal Products http://www.medicinesforeurope.com/wp-content/uploads/2016/03/biosimilars_report_en.pdf (accessed Sept 5, 2017)

Situation #2: Pharmacist initiated

2. When a physician writes a prescription for an originator biologic, but a **pharmacist** substitutes an interchangeable biologic instead
 - US states (not FDA) regulate this activity through state laws
 - Communication required to physician after drug is dispensed (timing and method defined by states)
 - In the EU, pharmacy-initiated switches are called “substitution” and are a decision made by individual countries

To dispense a biosimilar: Pharmacist must call in advance and get permission

To dispense an interchangeable biologic: Pharmacist does not need to obtain permission in advance, but many states will have a requirement to notify physician after drug is dispensed

<http://www.biosimilarsforum.org/biosimilars-insights/biosimilars-faqs> (accessed Sept 5, 2017)

European consensus Information Paper 2013. What you need to know about Biosimilar Medicinal Products http://www.medicinesforeurope.com/wp-content/uploads/2016/03/biosimilars_report_en.pdf (accessed Sept 5, 2017)

Substitution vs. Interchangeability

Don't forget: Most basic ground rule

Physicians can always prescribe whatever drug they believe is most suitable

Substitution (as defined in the US)

- Generally refers to the practice of utilizing one drug in place of another.
- Physicians can elect to substitute Drug #2 (e.g. a biosimilar) for a patient that previously received Drug #1 (e.g. originator)
- Pharmacists must obtain approval from the prescriber before dispensing another biologic

Interchangeability

- An additional designation granted by FDA to a biosimilar, based on additional data that is different than that required to obtain biosimilarity
- Pharmacists can dispense an interchangeable biologic in place of a prescribed originator WITHOUT first obtaining approval from the prescriber

NOTE: The US is the only country to have an “interchangeability” designation

What is an Interchangeable Biologic ?

Legal basis for “biosimilarity” and “interchangeability”

- The terms “biosimilar” and “interchangeable biologic” are both explicitly defined in the Biologics Price Competition and Innovation Act of 2009 (BPCIA)
- Signed into law in March 2010 as a part of the Affordable Care Act

Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act

U.S. legislative language defining “biosimilar”

Section 351(i) of the PHS Act defines *biosimilarity* to mean:

1. **“that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components”**

and that

2. **“there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”**

Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act

U.S. legislative language defining “interchangeability”

—Upon review of an application submitted under this subsection or any supplement to such application, the Secretary shall determine the biological product to be interchangeable with the reference product if the Secretary determines that the information submitted in the application (or a supplement to such application) is sufficient to show that—

1. “(A) the biological product — “(i) **is biosimilar to the reference product;**”
2. and “(ii) can be **expected to produce the same clinical result as the reference product in any given patient;**” and
3. “(B) for a biological product that is administered more than once to an individual, **the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product** without such alternation or switch.”

Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act

Does an interchangeable biologic need to be more “highly similar?”

NO !

There is no requirement that an interchangeable biologic - when compared to a biosimilar – be more pure or more closely match the reference product

- Claims to the contrary are misinformation -

IN FACT: If a biosimilar molecule were to be further refined in some manner, it would no longer be the same molecule and would need to be assessed by the FDA as a new biosimilar

AS A RESULT: A biosimilar and the corresponding interchangeable biologic are the SAME molecule

What happens when a biosimilar is designated to be an “interchangeable biologic?”

Benefit to healthcare system: Potential cost savings or increased access because of competition

Benefit to manufacturers: The first biosimilar to a given reference product will get one year exclusivity of the interchangeability status

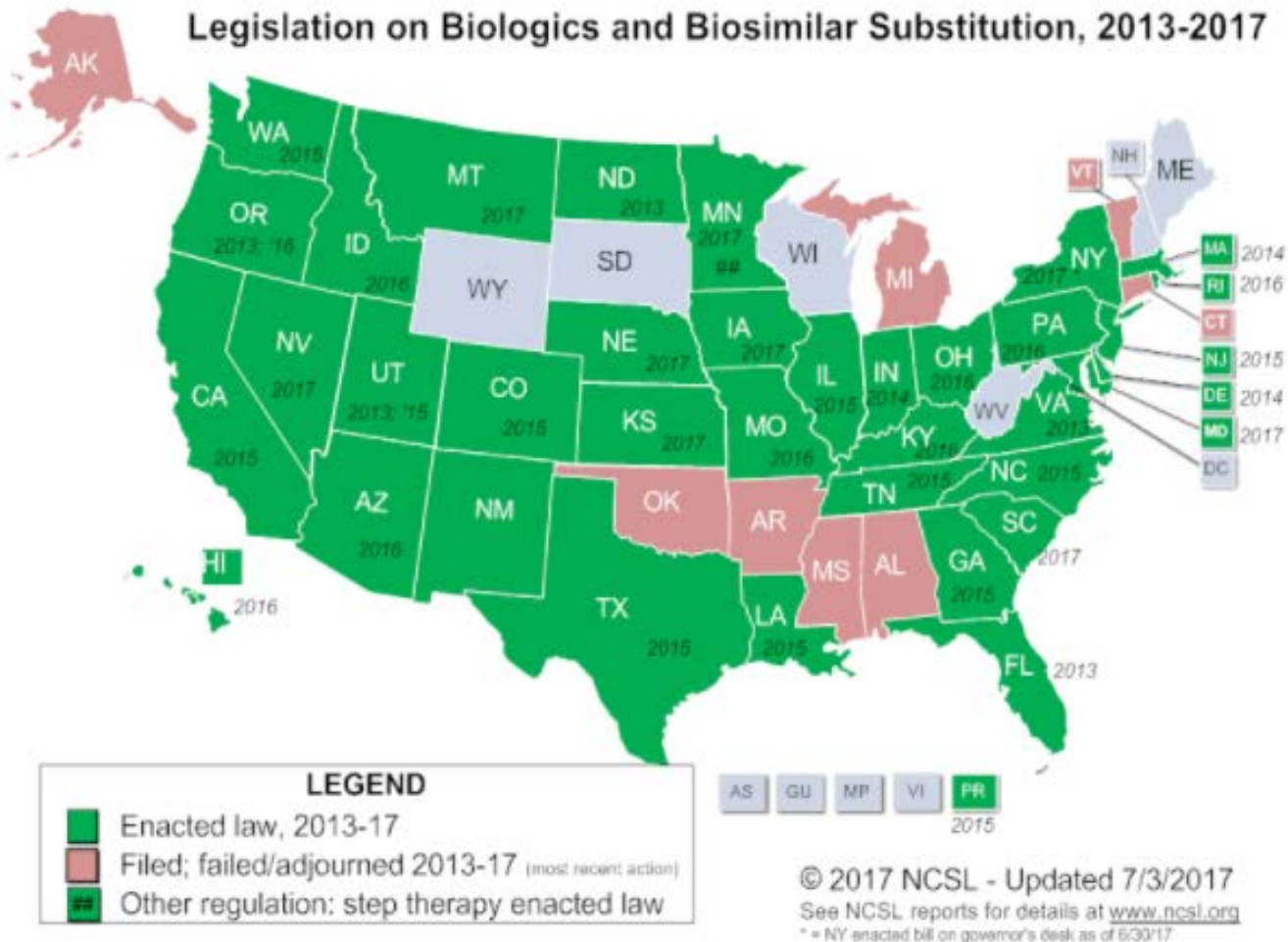
- During that year, no other biosimilar to the same reference product can be approved as an interchangeable biologic

State drug substitution laws must be modified to address biosimilar interchangeability

- State substitution laws were originally written for generic drugs, which are governed by the Food Drug and Cosmetic Act
 - Hatch/Waxman Act of 1984 (the Drug Price Competition and Patent Term Restoration Act) created a pathway for generic drugs based on bioequivalence to reference products
- Biological drugs are governed by the Public Health Safety Act
- Need to update drug substitution laws in each state to include biologics
 - Permit pharmacy-level substitution of an interchangeable biologic for a reference product

Many states have either passed or are considering legislation, but the enabling legislation is not yet in place in all states

State substitution laws



National Conference of State Legislatures: <http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx> (accessed Aug 22, 2017)

Common features of state biosimilar substitution laws

1. Must be a biosimilar that is approved by FDA as “interchangeable”
2. Prescriber able to prevent substitution by stating “dispense as written” or “brand medically necessary”
3. “Communication” after either reference product or interchangeable is dispensed
 - Timing varies (“5 days” to “reasonable time period”)
 - Could be via a notation in electronic medical records, PBM records or a pharmacy record that can be electronically accessible by the prescriber
4. Patient notification that a substitution or switch has been made
5. Records: The pharmacist and the physician must retain records of substituted biologic medications. Duration that records must be kept varies
6. Immunity: Some state legislation provides immunity for pharmacists who make a substitution in compliance with biologics state law
7. Web Lists: The state must maintain a public or web-based list of permissible interchangeable products
8. Cost or Pricing: Some state legislation requires that the lowest cost drug be dispensed

National Conference of State Legislatures: <http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx> (accessed Aug 22, 2017)

How can healthcare professionals and the public know if a biosimilar is designated as interchangeable?

- The “biosimilarity” and “interchangeability” status of a biosimilar is recorded in the Purple Book, an on-line database maintained by the FDA
 - Specific for biological drugs
 - Includes all originator biologics, irrespective of whether or not they are reference products
 - Includes biosimilars and interchangeable biologics
 - Includes therapeutic drugs, blood products and vaccines
- Analogous to but distinct from the Orange Book that is used for chemical drugs

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm> (accessed Aug 29, 2017)

Summary – Concept of interchangeability

- Think of “interchangeability” (or “interchangeable biologic”) as a noun
 1. A regulatory designation issued by FDA
 2. An interchangeable biologic is not a higher quality product
 3. Interchangeability is an additional data requirement - Manufacturers need to provide additional information different than that used to establish biosimilarity
 4. Not mandatory for a company to seek interchangeability for a biosimilar
 5. FDA maintains the “Purple Book,” an on-line database of the biosimilar/interchangeable status of all biological drugs

- Think of “substitution” as a verb
 1. Doctors always have the freedom to substitute a biosimilar in place of a reference product
 2. Pharmacists must contact a prescriber in advance if they want to substitute a biosimilar in place of a reference product
 3. However, if a biosimilar is designated by FDA as an interchangeable biologic, a pharmacist can substitute the interchangeable biologic for the RP without needing to first get a permission from the prescriber (subject to state laws)
 4. State laws govern post-dispensing communication, record-keeping and other aspects related to administration of interchangeable biologics

FDA Draft Guidance on Interchangeability Published in January 2017

Considerations in Demonstrating Interchangeability With a Reference Product Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ebla Ali-Ibrahim, 301-796-3691, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2017
Biosimilars

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf> (accessed Aug 29, 2017)

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Highlights of FDA Draft Guidance on Interchangeability

- Totality of evidence is basis for interchangeability
 - (a strong analytical data package will be considered in establishing clinical study expectations for interchangeability of a given biosimilar)
- Clinical switching study with PK/PD endpoints (efficacy, immunogenicity, safety supportive); ≥ 3 switches
- Use of US-licensed comparator
- Extrapolation to all indications, if scientifically justified
- Post-marketing data may be required as a part of an interchangeability application
- Where appropriate, non-inferiority statistical analysis in use error rate of the device (would require comparative human use studies)

Comments submitted by 53 stakeholders, including the AAM Biosimilars Council

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf> (accessed Feb 14, 2017)

<https://www.regulations.gov/document?D=FDA-2017-D-0154-0028> (accessed Aug 29, 2017)

No increased risk in safety or diminished efficacy

To address the legal requirement for:

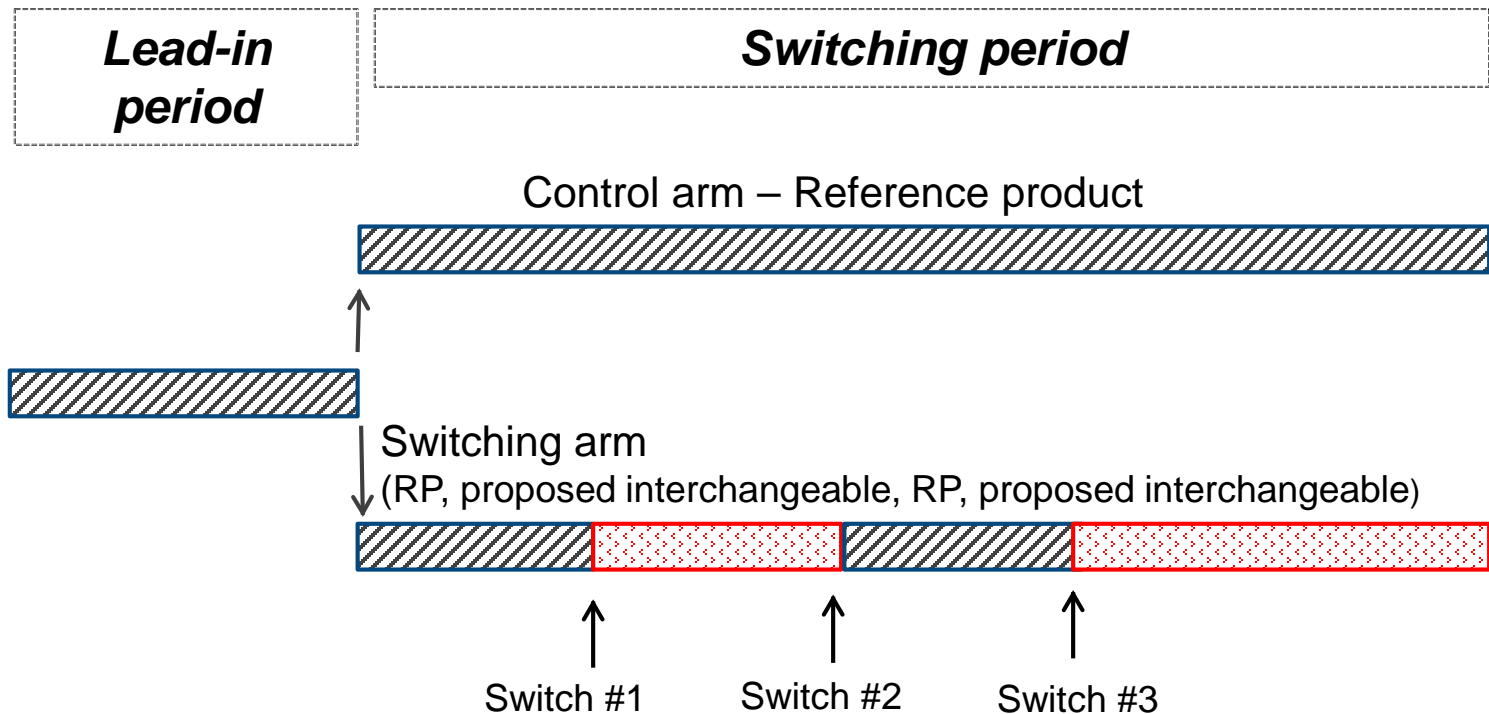
“the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product”



FDA is requiring a clinical switching that compares continued use of the reference product with alternating use of reference product and the proposed interchangeable biologic

Key features of the clinical study

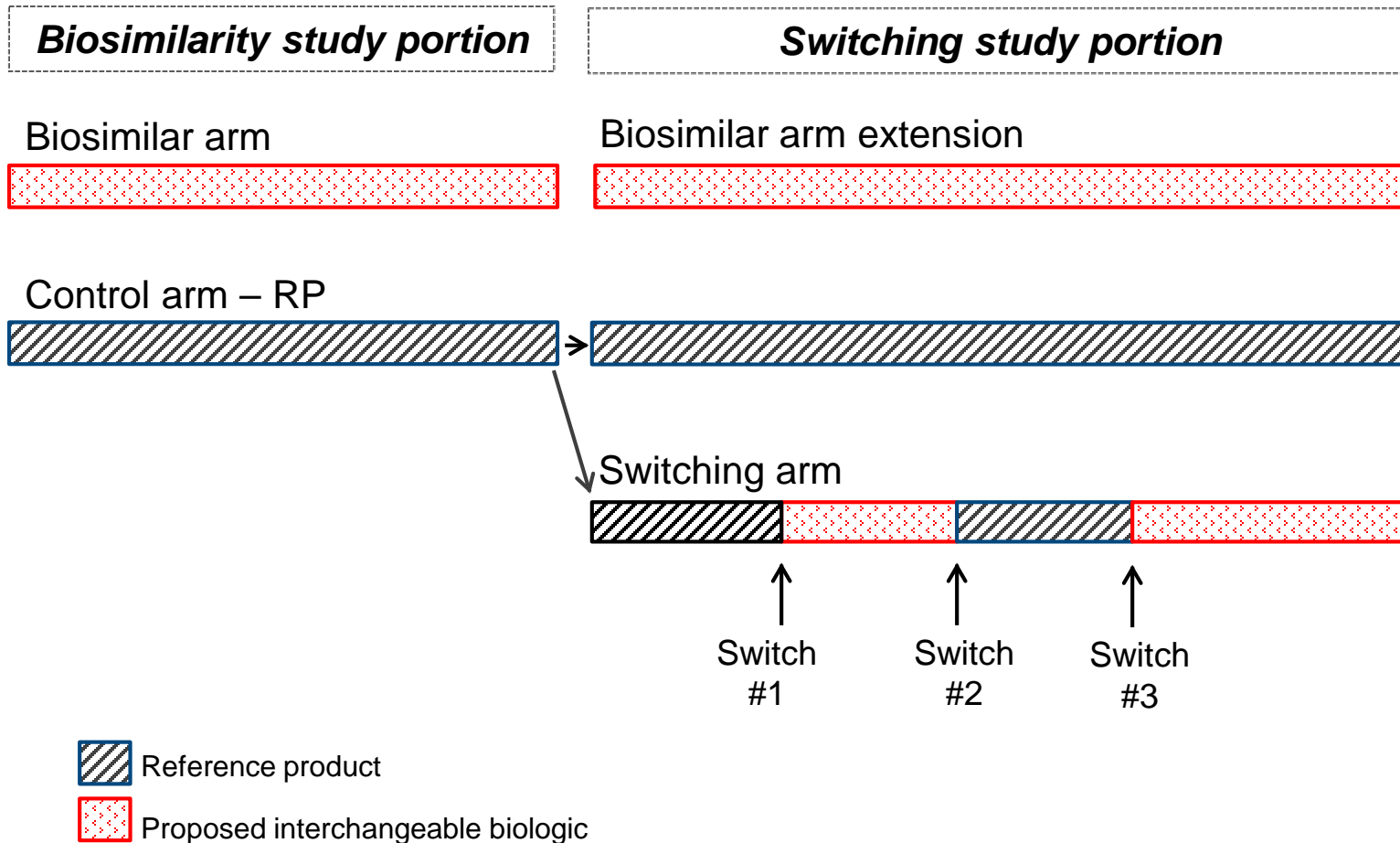
- Lead-in period of treatment with the reference product
 - Sufficient duration to ensure an adequate baseline (steady state PK)
- Randomized, two-arm period
 - Switching arm
 - Non-switching arm (reference product only)
- Number and duration of switches
 - Minimum of 4 treatment cycles to provide 2 separate exposure periods to each of the two products (at least 3 switches)
 - The last switching interval should be from the reference product to the proposed interchangeable product
 - Duration of exposure to the proposed interchangeable product after the last switch is sufficiently long to allow for washout of the RP (3 or more half-lives)
- Unlike biosimilarity PK studies that are preferentially conducted in healthy volunteers, FDA urges that interchangeability PK studies should be conducted in patients to mimic real-life use

Dedicated interchangeability study



-  Reference product
-  Proposed interchangeable biologic

Integrated study to establish both biosimilarity & interchangeability



PK Endpoints

FDA rationale for PK endpoints (discussed in the draft guidance)

- Most critical safety concern is immunogenicity (safety or loss of efficacy)
- Efficacy endpoints may not be sufficiently sensitive to detect impact of immunogenicity
- Lower PK (exposure) may reflect impact of immunogenicity

Challenges with PK endpoints

1. Underlying disease may impact PK, independent of immunogenicity
2. PK differences may not be clinically relevant
3. PK endpoints may not be relevant to some methods of administration

S Zheng, W Wang and H Zhou. "Impact of diseases, comorbidity and target physiology on ADME, PK and PK/PD of therapeutic biologics" in ADME and Translational Pharmacokinetics / Pharmacodynamics of Therapeutic Proteins: Applications in Drug Development and Discovery. H Zhou and F-P Thiel eds. (2016) J Wiley NJ.

Council requested that FDA be flexible in selection of endpoints

(Perhaps utilize direct measurements of immunogenicity, including neutralizing Abs)

Source of reference product

- FDA strongly urging that US-only reference product be used as the comparator for interchangeability studies
 - Stated concern is that there may be a difference between US- and ex-US RP that would only be detected after multiple switches
-

The Council questions this requirement:

- Analytical bridge for biosimilarity established that any differences that may exist are not clinically relevant
FDA Guidance: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product (April 2015)
- Originator biologics only have a single efficacy and safety data set
 - Originator showed that local variants in specifications, raw material sourcing, facilities or any structural/functional differences did not impact safety or efficacy
C Webster & G Woollett. Global Reference Comparator for Biosimilar Development. BioDrugs (May 2017) DOI 10.1007/s40259-017-0227-4

Council requested that FDA permit use of ex-US reference product if a scientific bridge is established to US material

Same clinical result in any given patient

To address the legal requirement for:

“...expected to produce the same clinical result as the reference product in any given patient”

FDA expects that sponsors will submit data and information consistent with the scientific justification for **extrapolation**

1. For which licensure as an interchangeable product is sought
2. For each condition of use for which the reference product is licensed

Use of extrapolation mirrors the use of the same concept for biosimilar approvals (Not necessary to study every single indication)

The Council welcomes application of extrapolation to interchangeability, but believes that FDA does not have authority to require data in indications not being sought

Is post-marketing data required as a part to the interchangeability data package?

It depends

1. No - for biosimilars to reference products that are known not to be inherently immunogenic
2. Perhaps yes - for biosimilars to reference products that are known to be inherently immunogenic
 - Subject to discussion between FDA and a manufacturer
 - If yes, would need to first be marketed as a biosimilar and would need to have sufficient use
 - If yes, no predefined size of post-marketing experience
 - Comparative immunogenicity of biosimilar and reference product in the initial data package would be a consideration

The potential requirement for post-marketing data as apart of an interchangeability application is of concern to the Council.

Interchangeability determinations should be made on the basis of analytical & functional and where necessary, clinical studies

Drug device presentations

FDA requesting comparative human factor studies of devices used to administer the RP and proposed interchangeable biologic

- Results to be subjected to statistical analyses

Requirement is of concern to the Council

- Human factor studies are designed to identify and evaluate use of the device, but not to establish an error rate
- Human factor studies identify and assess the criticality of an error to safe use, which is independent of an error rate

Council requested that the FDA reconsider requirements for quantitative human factor studies

Still to be addressed ...

- Naming of interchangeable biologics
 - Will the suffix of the proper name stay the same or be changed?
 - Not addressed in either the FDA's Final Guidance on biologics naming or in the Draft Guidance on interchangeability

- Labeling of interchangeable biologics
 - Will the label specify that the product is an interchangeable biologic or will this be left to inclusion in the Purple Book?
 - Not addressed in either the FDA's Draft Guidance on biosimilar labeling or in the Draft Guidance on interchangeability

Summary of draft guidance on interchangeability

Council supports:

1. Totality of evidence (and case-by-case approach) remains the cornerstone
2. Application of the concept of extrapolation
3. Clarity provided for the clinical study design
4. Post-marketing safety data, if available, may be useful

Council believes that further discussion is warranted on:

1. PK endpoints only
2. Ex-US reference standard
3. Requirement to justify all indications of the RP, even those for which approval is not sought
4. Potential to require post-marketing data as a part of an interchangeability application
5. Requirement for quantitative and comparative human factor studies of the delivery devices

Questions ?