# Omar Tounekti, MBA, MSc, PhD, Canada

- Acting Manager, Monoclonal Antibodies Division, Biologics and Genetic Therapies Directorate (BGTD), Health Canada

**GaBI Educational Workshops**

23 June 2019, G Hotel, Penang, Malaysia

2nd ASEAN Educational Workshop on
**REGULATORY CONSIDERATIONS FOR BIOSIMILARS**

# Analytical studies used to support biosimilarity in biological drug submission – a regulator's perspective

Omar Tounekti, MBA, MSc, PhD

23 June 2019

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# Analytical studies used to support biosimilarity in biological drug submission; a regulator's perspective

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Dr Omar Tounekti, A/Manager of the Monoclonal Antibodies Division
Biologics and Genetic Therapies Directorate
Health Canada

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# Disclaimer

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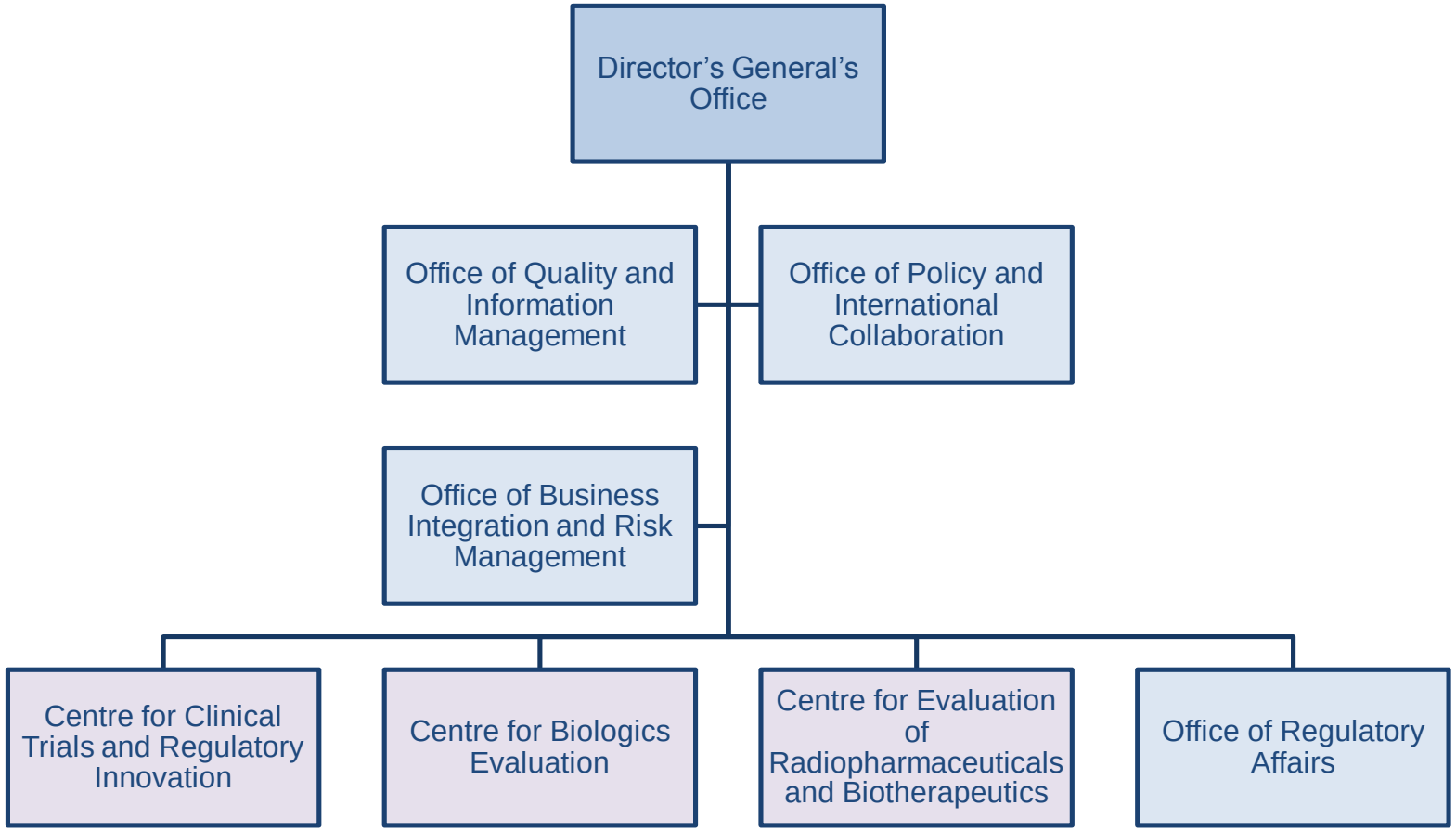
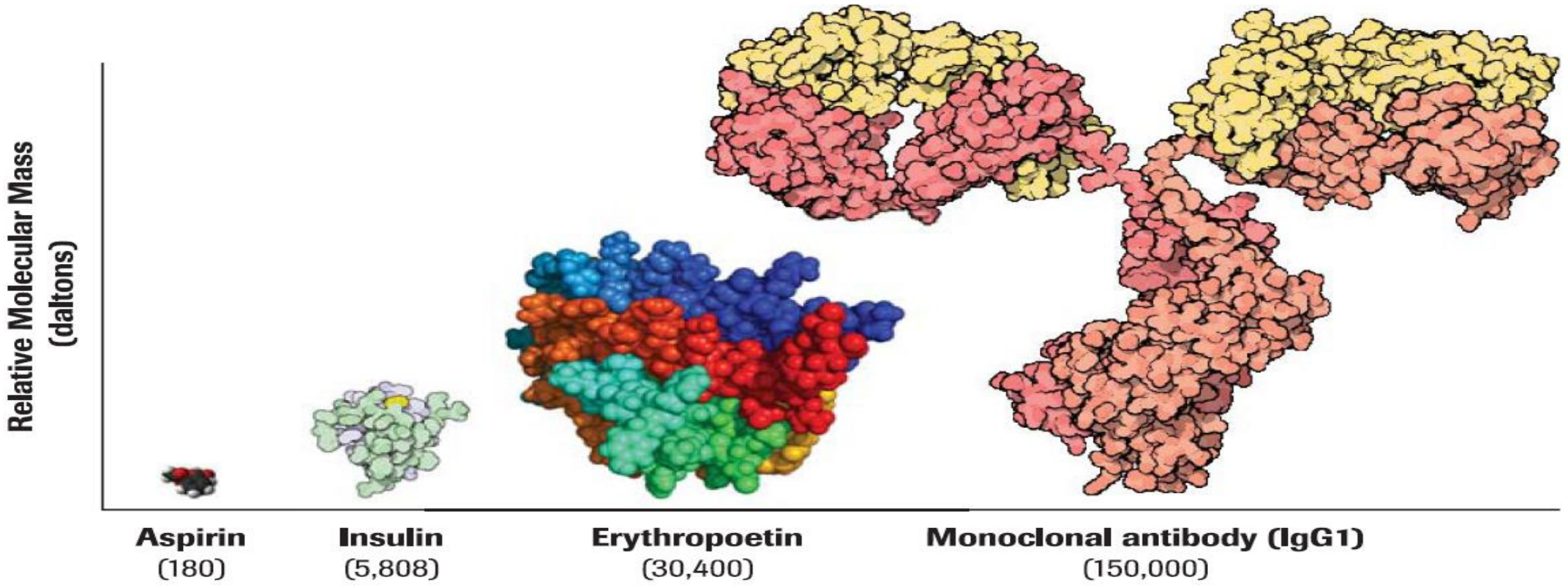
# Overview

- Introduction
- Chemistry and Manufacturing review of biosimilarity in practice
- Case study
- Conclusion

# Biologics and Genetic Therapies Directorate (BGTD)



# Chemical Drugs vs. Biologics




Ref: Revers and Furczon, CPJ, 2010, 143:134 - http://cph.sagepub.com/content/143/3/134

# The product is the process!

- Production by a living organism (microorganism, or plant or animal cells)
- Intricacy of the manufacturing process (raw materials, upstream, downstream)
- Inherent complexity of the product

→ Biologics can be sensitive to very minor changes in the manufacturing process

# What is a Biosimilar Biologic Drug?

- A biosimilar is a biologic drug that enters the market subsequent to a version previously authorized in Canada, and has demonstrated similarity to a reference biologic drug.

- Similarity is demonstrated by extensive structural and functional studies, complemented by non-clinical and clinical studies.

- Biosimilars are not generic biologics
  - Unlike generics, biosimilars are not pharmaceutically equivalent to their reference drugs.

# What is a Reference Biologic Drug?

- Biologic drug authorized on the basis of a complete quality, non-clinical, and clinical data package, to which a biosimilar is compared to demonstrate similarity.
  - accumulated adequate safety, efficacy, and effectiveness data in the post market setting such that the demonstration of similarity will bring into relevance a substantial body of reliable data.
  - a non-Canadian sourced version may be used as a proxy for the Canadian drug in the comparative studies.

# Canadian Regulatory Approach

- Biosimilars are regulated as new biologic drugs in Canada; they are subject to the *Food and Drugs Act* and Part C, Division 8 of the *Food and Drug Regulations* just like other new biologic drugs.

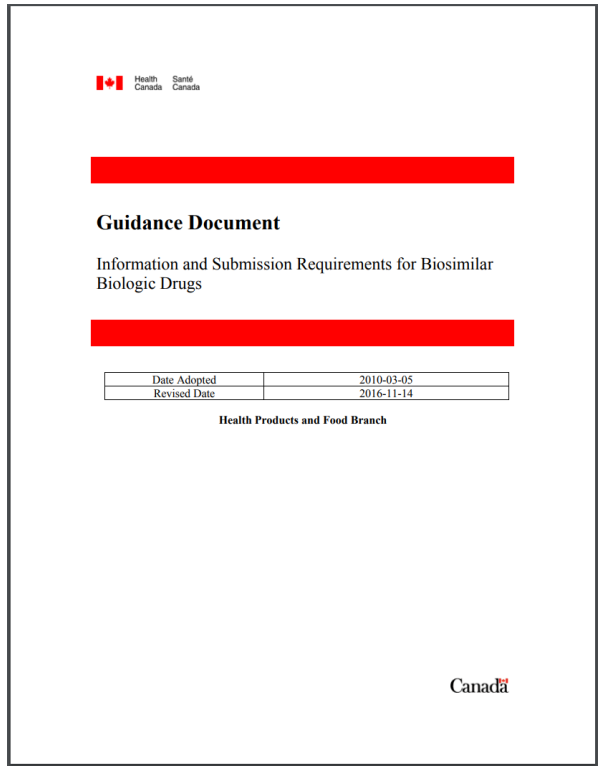
- Flexibility under existing framework allows for the regulation of biosimilars using the concept of similarity.

***"C.08.002(2) A new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug…"***


# Canadian Regulatory Approach

- **Guidance Document for Biosimilar Biologic Drugs**

  Health Canada published a guidance document in 2010 to communicate submission requirements to biosimilar sponsors. A revised Guidance was released in December 2016 to reflect experience gained by Health Canada over the last 6 years.


Health Canada Santé Canada

**Guidance Document**

Information and Submission Requirements for Biosimilar Biologic Drugs

| | |
|---|---|
| Date Adopted | 2010-03-05 |
| Revised Date | 2016-11-14 |

**Health Products and Food Branch**

Canada

- Authorized biosimilar biologic drugs are independent product. Once the NOC has been granted, there is no regulatory requirement to repeat the demonstration of biosimilarity against the reference product.

# Quality Review

- The biosimilar submission should include extensive data demonstrating similarity with the reference biologic drug.
- This should include characterization studies conducted in a side-by-side format.
- Similarity should be deduced primarily from comprehensive and well rationalized quality studies.

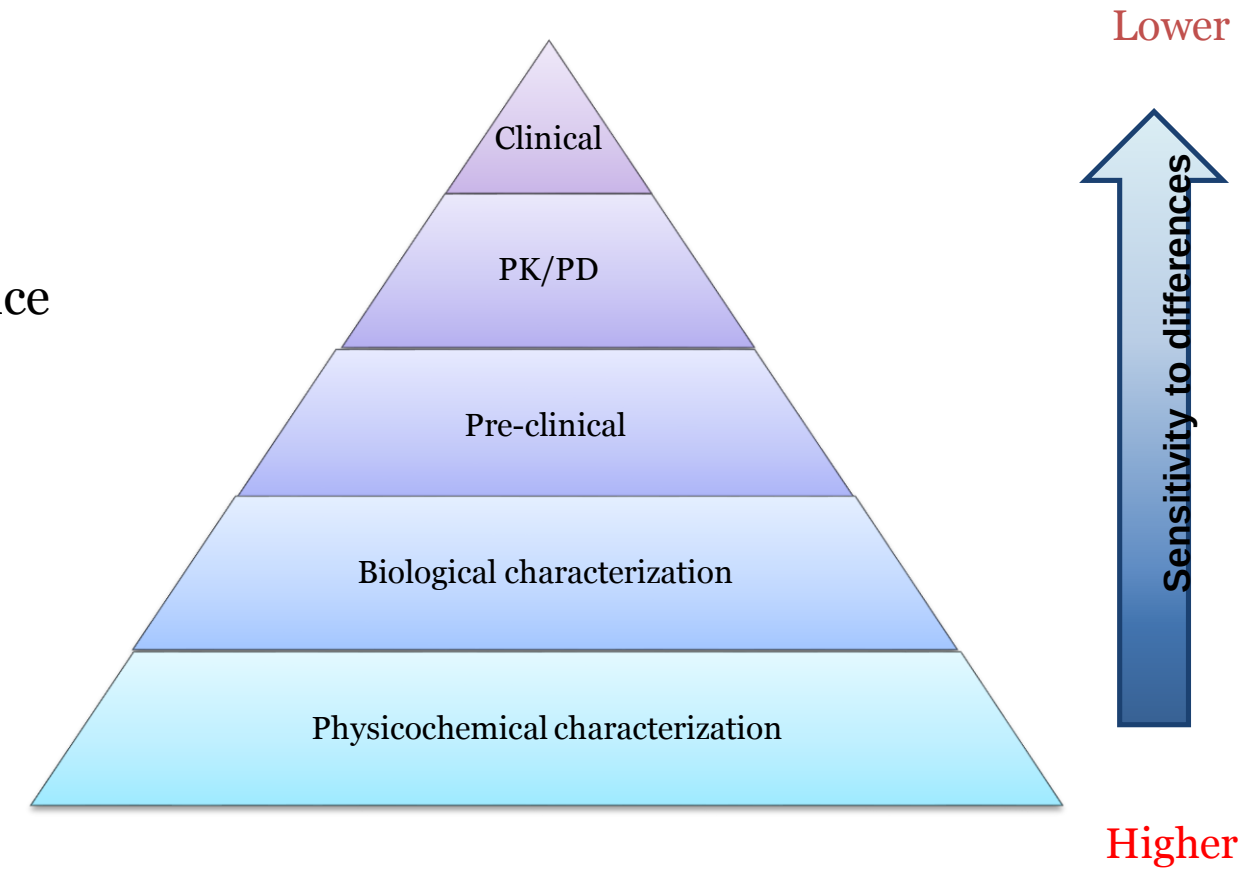
# Comparative analytical assessment is the foundation of biosimilars

- Quality by Design approach – risk assessment tool

- Critical Quality Attributes – high risk

- Non-critical attributes – greater tolerance

- State of art analytical tools: orthogonal methods

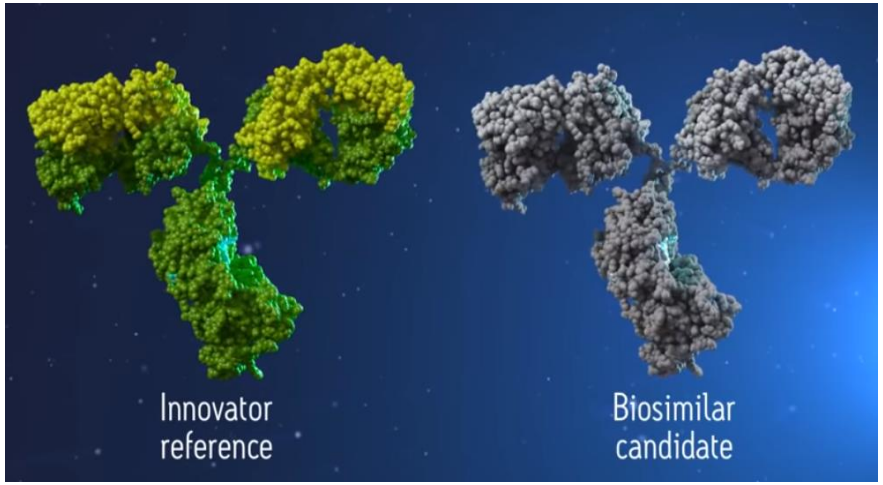


# Determination of biosimilarity

The demonstration of similarity does not signify that the quality attributes of the two products being compared are identical, but that they are highly similar with two consequences:

1) existing knowledge of both products is sufficient to predict that any differences in quality attributes should have no clinically meaningful impact

2) non-clinical and clinical data previously generated with the reference biologic drug are relevant to the biosimilar.




Ref.: https://www.waters.com/waters/en_CA/Biosimilars/nav.htm?cid=134751091&alias=Alias_biosimilars&locale=en_CA

# Fundamental Concepts

- Biosimilars are not “generic biologics” and many characteristics associated with the authorization process and marketed use for generic pharmaceutical drugs do not apply.

- Authorization of a biosimilar is not a declaration of pharmaceutical and/or therapeutic equivalence to the reference biologic drug.

- Once a Notice of Compliance (NOC) is granted, the biosimilar is a new biologic drug and regulated like any other new biologic drug.

# Approach to Quality Biosimilarity

- ICH Q5E

  The demonstration of comparability does not necessarily mean that the quality attribute of the pre-change and post-change products are identical; but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.

# Comparative Stability Profile

- Stability data, including from accelerated or stress conditions, can provide insight into potential product differences in the degradation pathways of the drug product and, hence, potential differences in product-related substances and product-related impurities.

- Side-by-side comparative stability studies with samples matched, as far as possible, with respect to date of manufacture may be able to detect subtle differences that are not readily detectable by the characterisation studies.
  - *e.g.*, trace amounts of protease detected by degradation over an extended time; or leachates from a container closure system causing activation of trace proteases

# Reference Product Batches

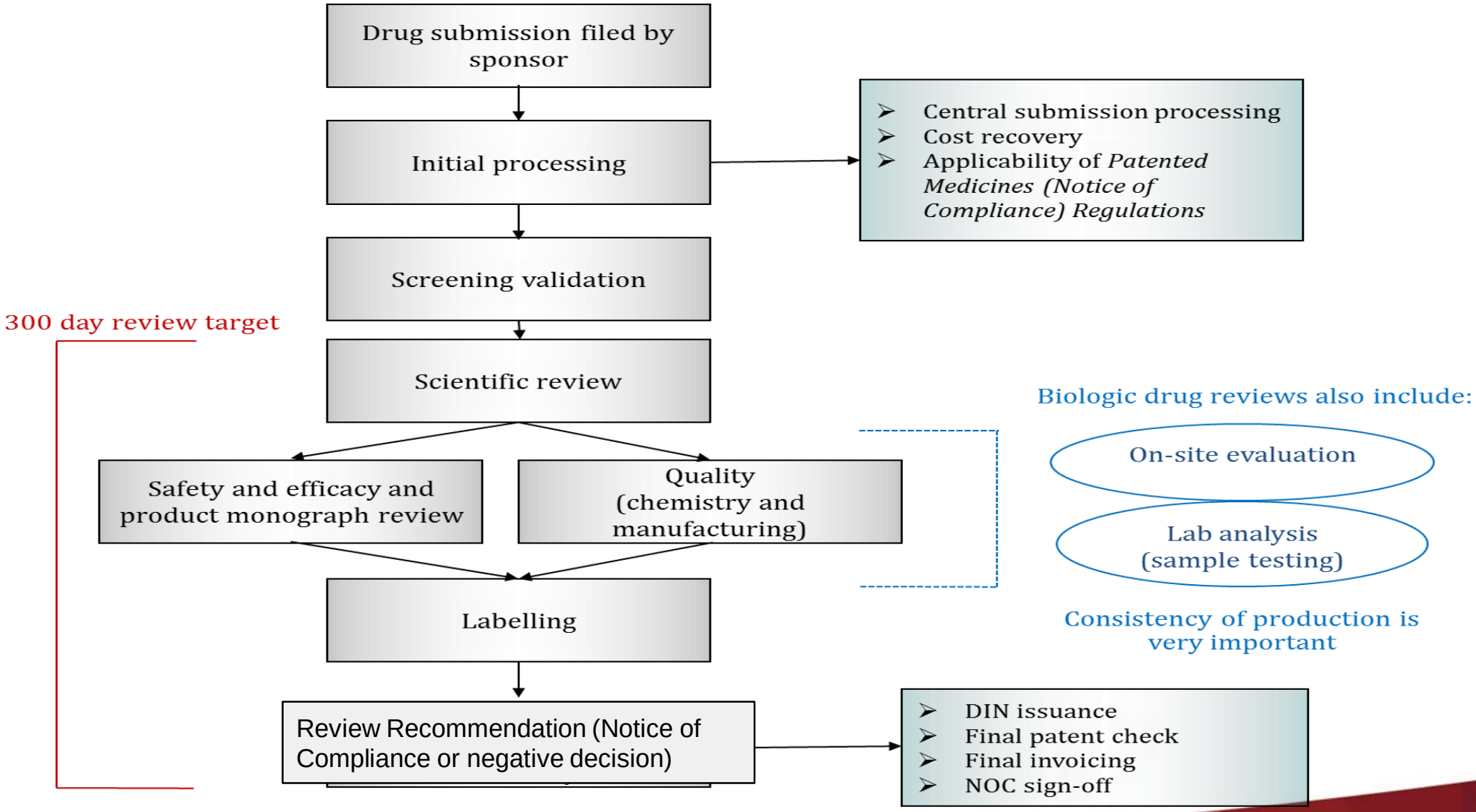
Data obtained from multiple batches of the biosimilar and of the reference biologic drug can help generate an understanding of ranges in variability.  This need not entail performing all tests on all batches; a matrix approach may be possible but should be rationalized.

Such data may be helpful when discussing with the regulatory authority evidence of a manufacturing process under control and appropriate ranges for critical quality attributes for the biosimilar

# Overview

Quality Review of Biosimilarity, in Practice

# New Drug Review Process – Biologics



# Review Plan

Gap Analysis

Areas of anticipated concern

Milestones (e.g. joint team meetings, Clarification Requests..)

OSE Determination

- OSE Determination form
- Risk assessment based on initial scan

Consistency lot testing determination

- Choice of test to be performed
  - Stability indicating

# Quality Target Product Profile

Risk-based approach to identifying the Critical Quality Attributes

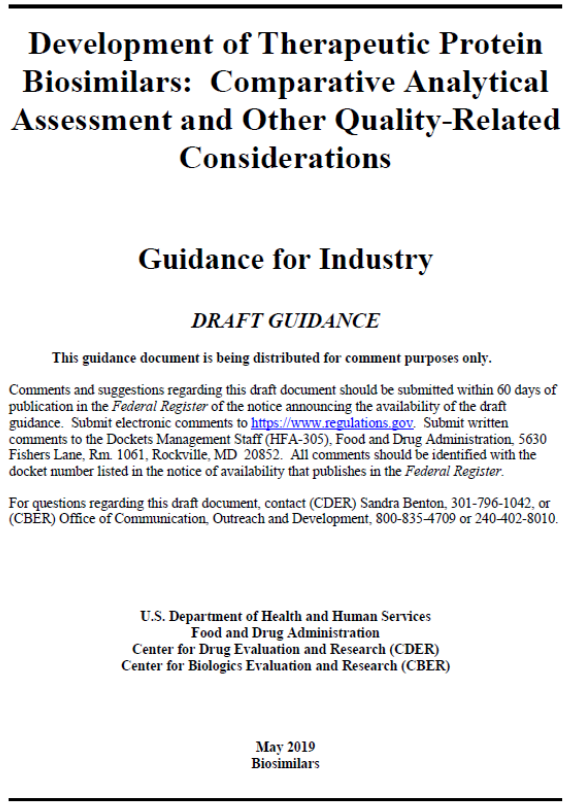
- Quality Attributes that are relevant to clinical outcomes (PK, PD, efficacy, safety)
    - Knowledge of mechanism of action
    - Publicly available information regarding the reference product
    - Knowledge from similar products
    - Experimental data
- Sufficient information should be provided to enable the review team to understand the analytical similarity approach and criteria

# Evaluation of Analytical Biosimilarity

- No Canadian requirement to use any specific statistical approach
- Expectation that the approach taken be appropriately justified
- Regardless of the approach taken, include plots of the biosimilarity data

# Analytical Similarity Evaluation

- No globally accepted approach
- FDA guideline: Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations (May 2019)
  - Ranking quality attributes based on risk assessment and statistical analysis
  - This is an acceptable approach for the BGTD



**Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations**

**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 https://www.regulations.gov. Submit written comments to the Dockets Management Staff (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) Sandra Benton, 301-796-1042, 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)**

**May 2019**
**Biosimilars**

# Biosimilarity Assessment

Methods used should be appropriate, fit-for-use

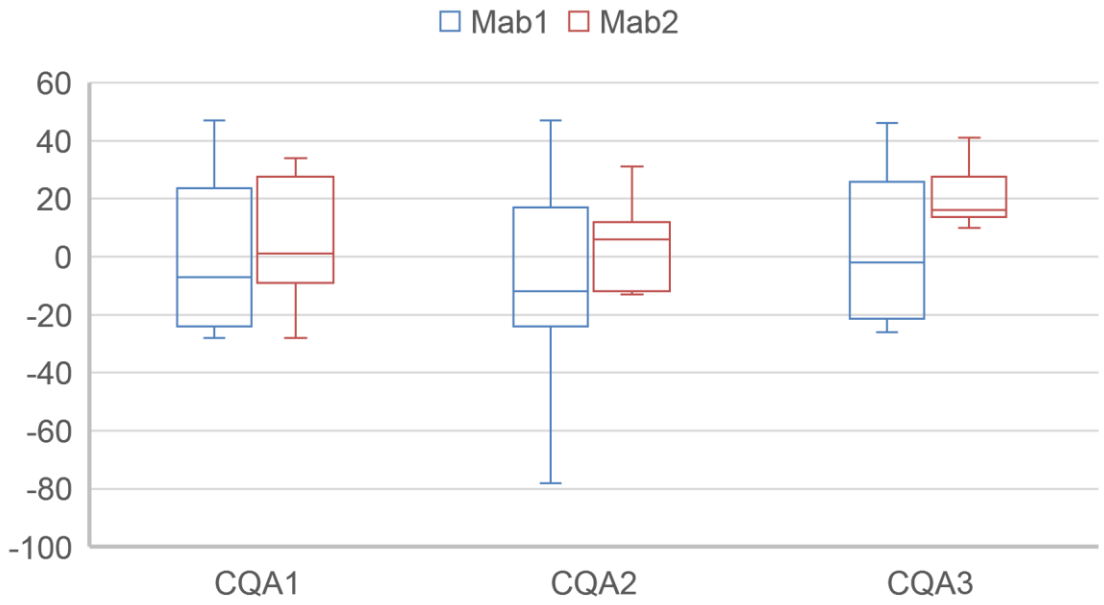
Ideally drug product samples should be compared

If formulation interferes with assay performance deformulation studies required

Comprehensive comparability assessment is expected

Orthogonal methods to assess each attribute

# Case Study



# Case study exercise

| Quality attribute | Product | Min/max ranges | Bar diagram |
|---|---|---|---|
| G0F-GlcNac | RBP A<br>SBP candidate 1 | 0.05 – 0.3 %<br>0.00 – 0.2 % |  |
| G0 | RBP A<br>SBP candidate 1 | 1.2 – 2.1 %<br>1.5 – 2.0 % |  |
| G0F | RBP A<br>SBP candidate 1 | 20.3 – 32.1 %<br>25.3 – 33.0 % |  |
| Man5 | RBP A<br>SBP candidate 1 | 0.0 – 0.9 %<br>0.2 – 0.5 % |  |
| (1,6)G1F | RBP A<br>SBP candidate 1 | 2.5 – 4.1 %<br>3.0 – 3.9 % |  |
| (1,3)G1F | RBP A<br>SBP candidate 1 | 1.6 – 2.3 %<br>1.7 – 2.2 % |  |
| G2F | RBP A<br>SBP candidate 1 | 10.5 – 25.7 %<br>11.0 – 24.4 % |  |
| G2FS1 | RBP A<br>SBP candidate 1 | 35.3 – 39.1 %<br>36.2 – 38.5 % |  |
| G2FS2 | RBP A<br>SBP candidate 1 | 11.4 – 13.2 %<br>11.4 – 13.0 % |  |
| NGNA | RBP A<br>SBP candidate 1 | 3.3 – 5.5 %<br>1.1 – 2.0 % |  |
| Deamidation | RBP A<br>SBP candidate 1 | 0.9 – 2.4 %<br>0.3 – 1.5 % |  |
| Oxidation | RBP A<br>SBP candidate 1 | 1.2 – 4.3 %<br>1.0 – 4.1 % |  |
| Dimer | RBP A<br>SBP candidate 1 | 0.0 – 2.1 %<br>0.0 – 0.8 % |  |
| Higher aggregates | RBP A<br>SBP candidate 1 | 0.0 – 0.8 %<br>0.0 – 0.2% |  |
| Binding assay | RBP A<br>SBP candidate 1 | 91 – 108 %<br>93 – 105 % |  |
| CDA activity | RBP A<br>SBP candidate 1 | 84 – 110 %<br>90 – 111 % |  |
| ADCC activity | RBP A<br>SBP candidate 1 | 75 – 132 %<br>82 – 115 % |  |

Quality attribute ranges of similar biotherapeutic product (**SBP**) **candidate 1** and reference biotherapeutic product (**RBP**) **A**, targeting a cell membrane bound target and where Fc functionality is an important part of the clinical mode of action.

The lengths of the bars show the relative widths of the quality attribute ranges. For attributes, showing a black line on the left, this black line represents the point of origin (i.e. 0%)

Ref: Schiestl, et al., Biologicals 42 (2014) 128-132

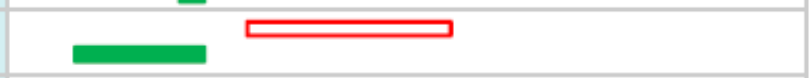
# Case study exercise

| Quality attribute | Product | Min/max ranges | Bar diagram |
|---|---|---|---|
| G0F-GlcNac | RBP A<br>SBP candidate 2 | 0.05 – 0.3 %<br>0.00 – 0.2 % |  |
| G0 | RBP A<br>SBP candidate 2 | 0.4 – 2.1 %<br>9.2 – 12.0 % | |
| G0F | RBP A<br>SBP candidate 2 | 20.3 – 32.1 %<br>25.3 – 33.0 % | |
| Man5 | RBP A<br>SBP candidate 2 | 0.0 – 0.9 %<br>0.2 – 0.5 % | |
| (1,6)G1F | RBP A<br>SBP candidate 2 | 2.5 – 4.1 %<br>3.0 – 4.2 % | |
| (1,3)G1F | RBP A<br>SBP candidate 2 | 1.6 – 2.3 %<br>1.5 – 2.0 % | |
| G2F | RBP A<br>SBP candidate 2 | 10.5 – 25.7 %<br>11.0 – 24.4 % | |
| G2FS1 | RBP A<br>SBP candidate 2 | 35.3 – 39.1 %<br>36.2 – 38.5 % | |
| G2FS2 | RBP A<br>SBP candidate 2 | 11.4 – 13.2 %<br>11.4 – 13.0 % | |
| NGNA | RBP A<br>SBP candidate 2 | 3.3 – 5.5 %<br>3.4 – 5.8 % | |
| Deamidation | RBP A<br>SBP candidate 2 | 0.9 – 2.4 %<br>0.3 – 1.5 % | |
| Oxidation | RBP A<br>SBP candidate 2 | 1.2 – 4.3 %<br>1.0 – 4.1 % | |
| Dimer | RBP A<br>SBP candidate 2 | 0.0 – 2.1 %<br>0.0 – 0.8 % | |
| Higher aggregates | RBP A<br>SBP candidate 2 | 0.0 – 0.8 %<br>0.0 – 0.2% | |
| Binding assay | RBP A<br>SBP candidate 2 | 91 – 108 %<br>93 – 105 % | |
| CDA activity | RBP A<br>SBP candidate 2 | 84 – 110 %<br>90 – 111 % | |
| ADCC activity | RBP A<br>SBP candidate 2 | 82 – 118 %<br>380 – 475 % | |

Quality attribute ranges of **SBP candidate 2** and **RBP A**, targeting a cell membrane bound target and where Fc functionality is an important part of the clinical mode of action.

Ref.: Schiestl, et al., Biologicals 42 (2014) 128-132

# Case study exercise

| Quality attribute | Product | Min/max ranges | Bar diagram |
|---|---|---|---|
| G0F-GlcNac | RBP B<br>SBP candidate 3 | 0.05 – 0.3 %<br>0.00 – 0.2 % |  |
| G0 | RBP B<br>SBP candidate 3 | 1.2 – 2.1 %<br>1.5 – 2.0 % |  |
| G0F | RBP B<br>SBP candidate 3 | 20.3 – 32.1 %<br>30.8 – 38.9 % |  |
| Man5 | RBP B<br>SBP candidate 3 | 0.0 – 0.9 %<br>0.2 – 0.5 % |  |
| (1,6)G1F | RBP B<br>SBP candidate 3 | 2.5 – 4.1 %<br>5.2 – 7.5 % |  |
| (1,3)G1F | RBP B<br>SBP candidate 3 | 1.6 – 2.3 %<br>3.0 – 3.2 % |  |
| G2F | RBP B<br>SBP candidate 3 | 10.5 – 25.7 %<br>5.3 – 7.2 % |  |
| G2FS1 | RBP B<br>SBP candidate 3 | 35.3 – 39.1 %<br>32.1 – 34.5 % |  |
| G2FS2 | RBP B<br>SBP candidate 3 | 11.4 – 13.2 %<br>9.7 – 11.6 % |  |
| NGNA | RBP B<br>SBP candidate 3 | 3.3 – 5.5 %<br>3.8 – 4.2 % |  |
| Deamidation | RBP B<br>SBP candidate 3 | 0.9 – 2.4 %<br>1.1 – 1.6 % |  |
| Oxidation | RBP B<br>SBP candidate 3 | 1.2 – 4.3 %<br>1.0 – 4.1 % |  |
| Dimer | RBP B<br>SBP candidate 3 | 0.0 – 2.1 %<br>0.0 – 0.8 % |  |
| Higher aggregates | RBP B<br>SBP candidate 3 | 0.0 – 0.8 %<br>0.0 – 0.2% |  |
| Binding assay | RBP B<br>SBP candidate 3 | 91 – 108 %<br>93 – 105 % |  |

Quality attribute ranges of **SBP candidate 3** and **RBP B**, targeting a soluble target and where Fc functionality is believed to be not relevant for the clinical mode of action.

Ref: Schiestl, et al., Biologicals 42 (2014) 128-132

# Biosimilarity Outcome

It is likely that not all parameters will be highly similar

The key is in the potential impact on clinical outcomes

Biosimilarity program should be designed to identify differences

The relevance of those differences should be explored experimentally and through prior knowledge to demonstrate that there is no impact on PK, PD, efficacy or safety

# Biosimilarity Outcome

- Expect that there will be differences
- Explain the differences.  Tell the story of your data.  Don’t be afraid of it.
- It is not useful to solely rely on potency measures to justify differences but it is reasonable to discuss the sensitivity of the assay in question and provide a logical discussion of the likelihood that the observed differences would have a clinical impact.
- Literature references are acceptable as part of the argument.

Thanks to colleagues in BGTD for the provision of slides in this presentation.