The Form and Substance of Higher Order Structure Studies Used to Support Comparability and Biosimilarity in Biological Drug Submission; a Regulator's Perspective

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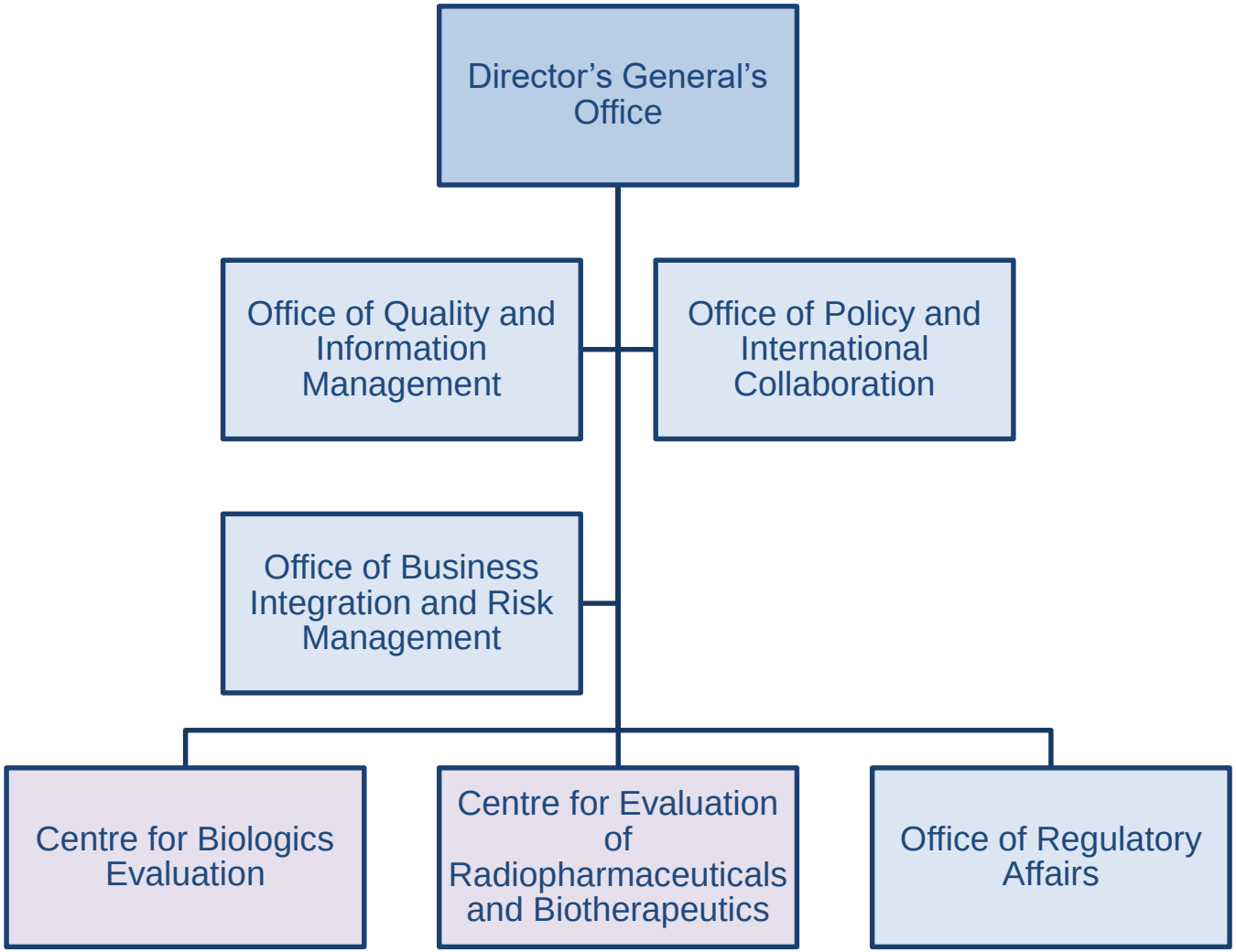
Presentation Outline

- Introduction
- HOS studies during product development
- HOS studies & the control strategy
- HOS studies to support comparability
- HOS studies to support biosimilarity
- Regulatory Perspective: other points to consider
- Conclusion

Biologics and Genetic Therapies Directorate (BGTD)

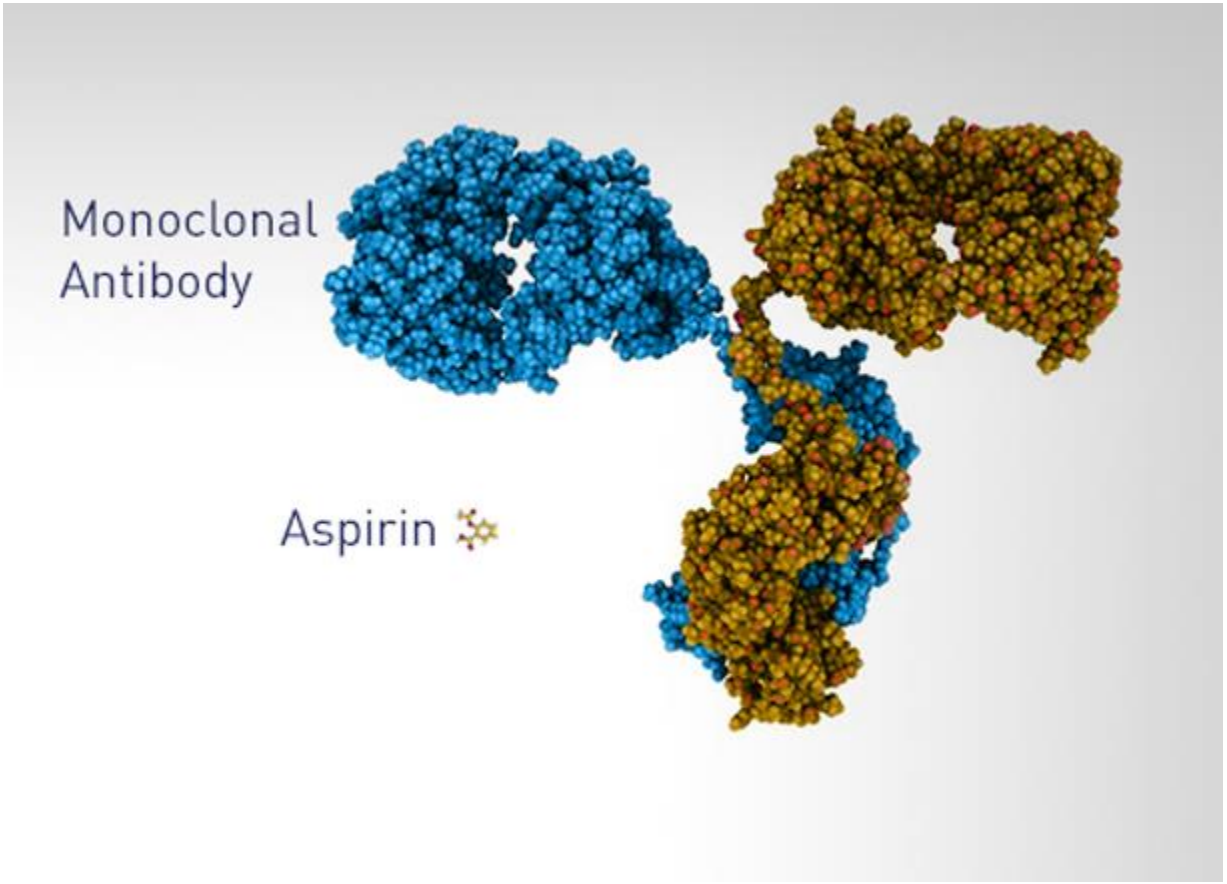


Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics

Chemistry and Manufacturing Review Divisions:

- Cytokines
- Hormones & Enzymes
- Monoclonal Antibodies
- Radiopharmaceuticals & Gene Therapies

Biologics are generally large and complex molecules.



Source: NIH

HOS analytical methods could have a significant value added throughout the product lifecycle

- Selection of the best candidate
- Process design
- Formulation development studies
- Characterisation studies
- Storage conditions (stability studies)
- Establishment of the appropriate control strategy (better risk assessment)
- Process consistency: comparability studies
- Investigation of deviations

Product development

Determination of product's HOS, including secondary and tertiary structure, mechanisms of aggregation and degradation, will increase the **knowledge of the structure/function relationship**.

HOS data may contribute to the assessment of risk for some product attributes and could allow the identification of drug substance critical quality attributes

ICHQ8 *Pharmaceutical Development*
*ICH*Q11 *Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)*

Product development

Analytical procedures used for determination of HOS are an important element of the Quality by Design approach:

- understanding the molecular structure of the biologic

- identification of risk and definition of CQAs

Control Strategy

- The physicochemical characterization program is important for setting the appropriate specifications.

- Heterogeneity of Biologics defines their quality, the degree and profile of this heterogeneity should be characterized, to assure lot-to-lot consistency. This includes information regarding higher-order structure of the desired product.

S.3 Characterization
Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

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

Comparability (Consistency of Manufacturing)

- Following a manufacturing process change, manufacturers should attempt to determine that higher order structure (secondary, tertiary, and quaternary structure) is maintained in the product.

- Use of orthogonal methods to evaluate the same quality attribute (e.g., molecular weight, impurities, secondary/tertiary structures) to maximise the possibility that differences in the product caused by a change in the manufacturing process might be detected.

Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process

Comparability (Consistency of Manufacturing)

- Determinations of product **comparability** can be based solely on quality considerations if the manufacturer can provide assurance of comparability through analytical studies

- The nature and the level of knowledge of the product is critical: relationship between physicochemical Characteristics, HOS and biological activities.

Biosimilarity

- *A final determination of similarity will be based on all relevant data from structural, functional, non-clinical and clinical studies.*

- *The comparative structural and functional studies will determine the type and extent of data to be derived from non-clinical and clinical studies on the drug product.*

Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs (Health Canada)

Biosimilarity

- *Analytical tests should be carefully selected and optimised to maximise the potential for detecting relevant differences in the quality attributes of the biosimilar and the reference biologic drug.*

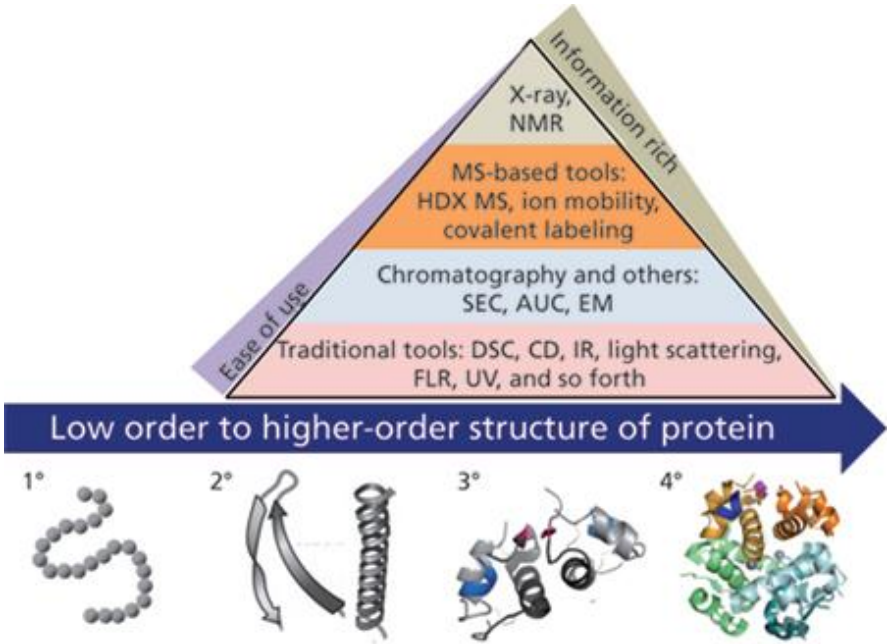
- *The manufacturer should attempt to determine that the higher order structure (secondary, tertiary, and, where applicable, quaternary) is comparable. If appropriate higher order structural information cannot be obtained, a relevant biological activity assay (see biological activity below) could indicate a correct conformational structure.*

Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs (Health Canada)

Regulatory Perspective: points to consider

Analytical procedures used for HOS studies have a very high potential

New analytical technology and modifications to existing technology are continually being developed and should be utilized when appropriate.



Source: Joomi Ahn, St. John Skilton, LCGC North America, Volume 31, Issue 6, pg 464–471

Regulatory Perspective - Points to Consider

- The measurement of quality attributes in characterisation studies does not necessarily entail the use of validated assays but the assays should be scientifically sound and provide results that are reliable (ICH Q5E).

- Challenge to include certain HOS analytical procedures in the control strategy

Regulatory Perspective: Points to Consider

– HOS techniques are more complex than other conventional characterization methods: Include description of important features such as sensitivity (resolving power), variability, robustness and limitations of the HOS technique

– Several studies in different sections of the file, absence of a document to tell the story:

What do these results mean?

Source: https://visme.co/blog/how-to-tell-stories-with-data/

Conclusion

- Use of modern biophysical techniques to characterise and assess the HOS of biological therapeutics is a fundamental component of their development process and the regulatory file.

- Use of these techniques to demonstrate comparability following a manufacturing change and as part of the analytic similarity package for biosimilar is encouraged.

- Relevance of the results as well as key features, advantages and limitations of the techniques used to characterise and assess the HOS should be well explained in the submission.

Acknowledgments

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THANK
YOU