Complex pharmaceutical health products: Abbreviated New Drug Submission (ANDS) of injectable synthetic peptides where the Canadian Reference Product is a peptide of rDNA origin

CAPRA Education Day 2026

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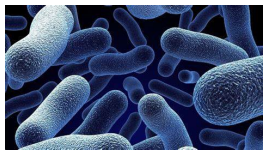
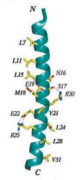
Outline

- Overview of the Canadian Regulatory Framework
- Demonstrating Active Pharmaceutical Ingredient (API) Sameness
- Impurities and Immunogenicity Risk
- Bioequivalence
- Drug-Device combination products
- Common Deficiencies and Recommendations
- Transparency

Canadian Regulatory Framework



Biologic drugs



(Reviewed by Biologic and Radiopharmaceutical Drugs Directorate)

Innovator drugs produced by recombinant DNA (rDNA) technologies

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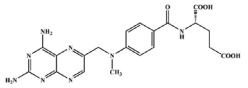
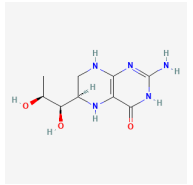
Biosimilar

Synthetic drugs





(Reviewed by the Pharmaceutical Drugs Directorate)

Innovator drugs produced by chemical synthesis

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Copy of the drug

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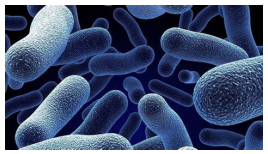
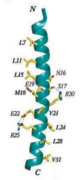
Generic

Blurring the line: Synthetic Peptides Based on rDNA Technologies



Biologic drugs



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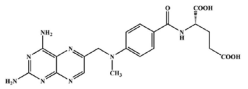

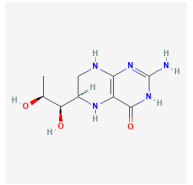

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Innovator drugs produced by chemical synthesis

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Generic

Copy of the drug

Abbreviated New Drug Submission (ANDS)

Pharmaceutical equivalence with the corresponding Canadian Reference Product (CRP)

Chemical characterization and comparative physicochemical studies

Conditions of use

Conditions of use for the proposed drug fall within the conditions of use for the CRP

Bioequivalence

Needs to be established with the CRP based on pharmaceutical and, where necessary, bioavailability characteristics

Same route of administration

For drug-device combination products: Needs to be substitutable with the innovator without additional training or intervention of a health care provider

New Drug Submission (NDS)

If a proposed generic product differs significantly from the CRP, then the appropriate route for filing is through a NDS.

In the case of synthetic peptides, the NDS would be reviewed by PDD

Regulatory Guidance

No Canadian-specific regulatory guideline for generic synthetic peptides where the Canadian Reference Product is a peptide of rDNA origin

Health Canada follows the scientific advice articulated in the US-FDA May 2021 guidance, "ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin".

US-FDA Product Specific Guidances (PSG) Draft Guidances for Generic Drug Development (e.g., liraglutide, semaglutide, glucagon)

Any updates by the US-FDA to guidances will be reviewed for consideration by Health Canada.

Demonstrating Active Pharmaceutical Ingredient (API) Sameness

- Primary Sequence and Physicochemical Properties
- Secondary Structure
- Higher Order Structure including Oligomer/Aggregation States
- Biological Activities

Demonstrating Active Pharmaceutical Ingredient (API) Sameness

Extensive physicochemical and biological characterization	Characterization	3D structural comparability	Statistical analysis
The use of higher-resolution and orthogonal analytical methods to compare the proposed generic product and the CRP	Nuclear Magnetic Resonance (NMR) is a baseline expectation for the characterization of peptides	Analytical methods used for higher order structure and aggregation state should be appropriately validated or qualified to ensure sensitivity to structural changes.	Includes the use of pre-specified, scientifically justified acceptance criteria, appropriate sample sizes, and statistical methods that can distinguish true product-related differences from normal analytical variability

Comparative characterization data should be provided on samples at the end of the proposed shelf life, including any proposed in-use period

Biological Activity

Functional equivalence can be demonstrated through *in vitro* or animal studies.

Example: Bioassay which is an *in vitro* assay to measure the biological activity of the proposed drug

- Based on activation of a receptor expressed at the cell surface of cells in culture and measurement of a molecule produced following receptor activation, often cAMP

Studies have to be fit for purpose, validated and constructed appropriately

- Details of the biological assay including the validation and protocol are reviewed

Comparison of a minimum

- 3 drug product (DP) batches at or close to release
- 3 DP batches at or close to end of shelf life
- 3 unexpired batches of the CRP

Peptide-Related Impurities and Immunogenicity Risk

Peptide-related impurities can differs based on the manufacturing process

rDNA technologies

Synthetic production (next slide)

Host cells proteins and peptides

Proteolysis

Enzymatic modifications

Chemical modifications

Synthetic Peptides Impurities: Process-Related Impurities

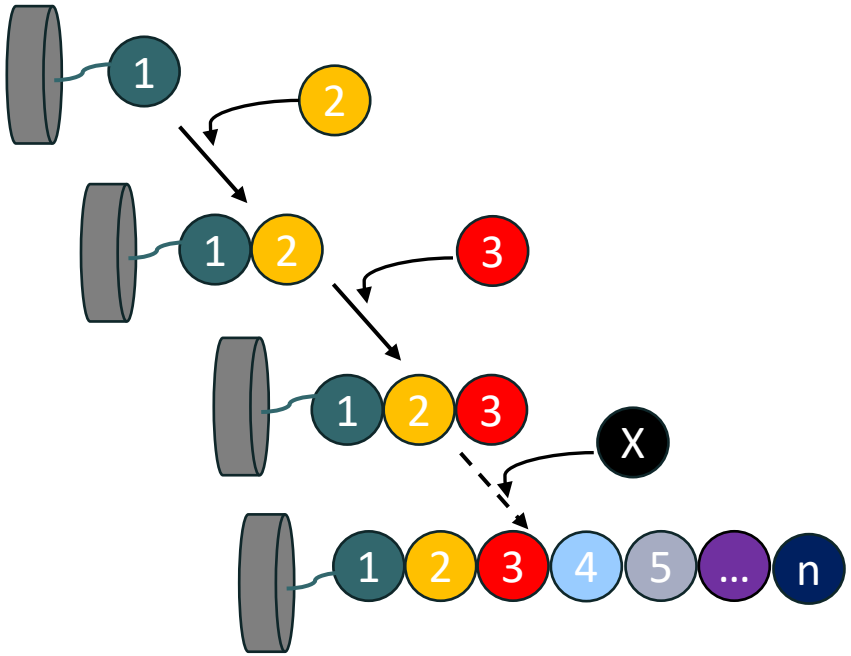
Process-Related Impurities include:

- residual solvent,
- reagents
- leachables and extractables
- elemental impurities

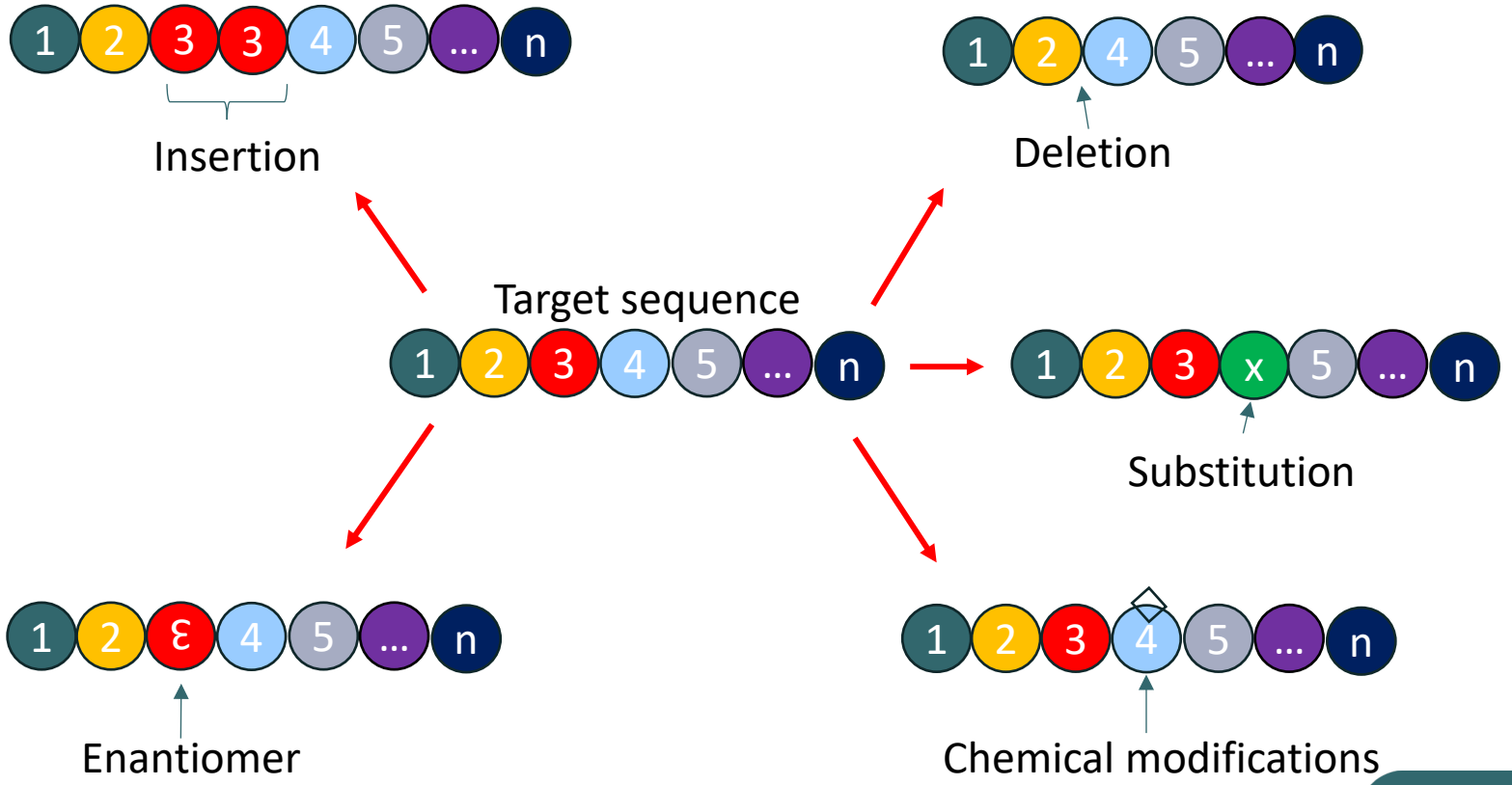
Should be characterised according to ICH Guidelines ICHQ3A – ICHQ3E

Synthetic Peptides Impurities: Peptide-Related Impurities

Chemical Synthesis



Product-Related Impurities



FDA Guidance for Synthetic Peptides Based on rDNA Innovator

Comparison of product-related impurity profile of the generic and the rDNA-produced Reference Drug

- For specified impurities common to generic and CRP
  - Level proposed in generic ≤ CRP
- For any new impurities in the proposed generic or impurities ≥ CRP
  - ≤ 0.5% of the drug substance (individual impurities)
  - Impurities at 0.10% to 0.5% should be identified, characterized and tested for immunogenicity risk

Immunogenicity Risk Assessment Framework

Innate Immunity:

- Focuses on process-related impurities such as contaminants, aggregates, leachables.
- Conducted on the **fully formulated drug product** in comparison with the CRP
- Goal: ensure the generic does not contain substances that might cause a non-specific stimulation of the innate immune system
- 3 batches at or close to release, 3 batches at the end of shelf life and 3 batches of unexpired CRP.

Immunogenicity Risk Assessment Framework

Adaptive Immunity:

- For new or elevated peptide-related impurities (typically those at levels of 0.10% to 0.5%).
- Each of these impurities should be evaluated individually
- Goal: determine if the impurity could trigger a specific adaptive immune response, for instance, by creating new T-cell epitopes
- The use of orthogonal methods such as *in silico* and *in vitro* analyses are recommended.

Immunogenicity Risk Assessment Framework: Non-Clinical Assays

Innate Immune Response Modulating Impurities (IIRMI) Assays	Aggregation Studies	*In silico* Assessment	*In vitro* Cell-Based Assays
• assess the potential of the formulated drug product to stimulate innate immune activity compared to the CRP	• data should demonstrate that the generic product does not have a greater propensity to form aggregates • under stress conditions or under long term storage • aggregates can be immunogenic	• predict whether new impurity sequences have an increased binding affinity for Major Histocompatibility Complex (MHC) • Indication for potential to be a T-cell epitope.	• laboratory tests to experimentally measure MHC binding and T-cell activation or proliferation in response to the impurity

Assay validation reports must be submitted and demonstrate that the assay was fit for the intended purpose.

Bioequivalence

- Health Canada's Guidance "Pharmaceutical Quality of Aqueous Solutions" is not applicable to complex dosage forms
- Principles may be applied during the evaluation
- A waiver of the *in vivo* bioequivalence study may be requested based on satisfying criteria of similarity comparison between the Canadian Reference Product (CRP) and the test product.
- Consider the value of bioequivalence studies (including with PK and PD data when applicable)

Acceptability of the Biowaiver: Criteria

A quantitative comparison of the formulations of both the test product and the CRP

A comparison of physicochemical properties between the test product and CRP relevant to the quality and performance of the drug product and dosage form

A comparison of relevant medical device attributes between the test product and CRP

A qualitative and quantitative comparison between the test product and CRP for product-specific attributes, based on the scientific advice outlined in the US-FDA Guidance document (see slide 6)

Demonstration that the active pharmaceutical ingredient (API) of the CRP, as well as the synthetic API in the proposed product, are equivalent discrete (single) chemical entities.

Results from multiple orthogonal characterisation methods should be presented to demonstrate equivalency in Higher Order Structure and Aggregation profile.

- The higher order structure may impact the safety and efficacy of the proposed product.

Drug-Device combination products

- As per Health Canada Policy on Drug/Medical Device Combination Product
  - Combination product: A product that combines a drug component and a device component in a singular product
  - If the principal mechanism of action is achieved by pharmacological means: subjected to the *Food and Drug Regulation*

Drug-Device combination products: ANDS

The device should be compared to the device of the CRP

Health Canada relies on the scientific guidance provided in the U.S. FDA January 2017 draft guidance "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA".

The injection device of the generic product should be substitutable to the CRP without intervention from a health care professional and/or additional training.

Drug-Device combination products: ANDS

Differences between the proposed generic device and the CRP that may impact critical tasks could trigger the need for a Comparative Use Human Factors study.

Essential Performance Requirements study should consider the following (not exhaustive):

- forces required to remove and replace the pen cap
- the torque to install the needle and to dial the dose
- the force required to push the dose button

Container closure system should be evaluated from a quality perspective (e.g., leachables)

Common Deficiencies

- Inadequate Characterization Studies
- Improper Impurity Identification
- Unresolved Impurities
- Unjustified Higher Impurity Levels
- Elevated levels of Aggregates

Recommendations

- Consider all the requirements of an ANDS submission
- Follow the scientific advice articulated in the draft FDA PSG and in the US-FDA May 2021 guidance, "ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin”.
- Requesting pre-submission meetings well in advance of filing your submissions

Application

- Using the scientific and regulatory approaches described in this presentation, Health Canada has been reviewing numerous ANDS submissions of synthetic peptides where the Canadian Reference Product is a peptide of rDNA origin.

Generic Submissions Under Review

- Generic submissions under review (GSUR) list helps to make our review processes more transparent
- Each entry includes
  - medicinal ingredient(s)
  - therapeutic area
  - year and month the submission was accepted into review
  - company (sponsor) name for ANDSs accepted into review on or after April 1, 2024 only

(https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/generic-submissions-under-review.html)

Regulatory Decision Summaries

- Regulatory Decision Summaries (RDSs) explain Health Canada's decision for certain health products seeking market authorization.
- Include the purpose of the submission and the reason for the decision
- Available on the Drug and Health Product Portal
- https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/regulatory-decision-summary.html

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