KU LEUVEN



Biologicals of Biosimilars ?

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Biologicals (inclusief biosimilars)

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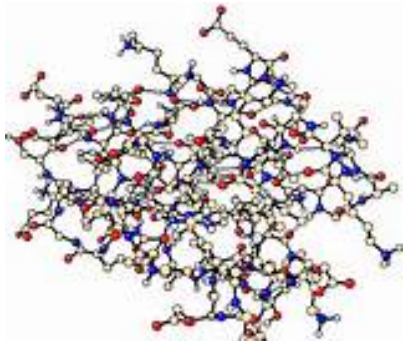
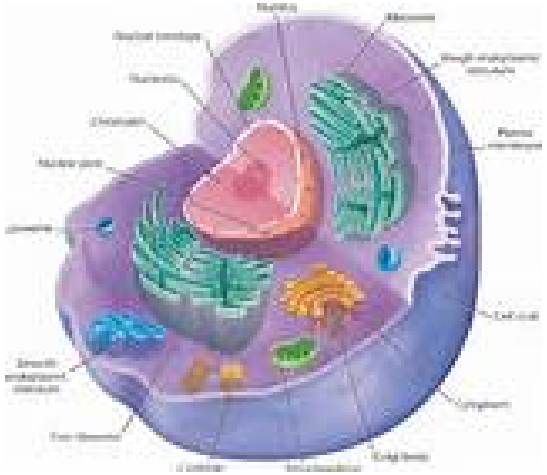
Biologisch geneesmiddel: definitie





Is een wel gekarakteriseerd biologisch product die geproduceerd wordt door middel van levende systemen zoals weefsel- of celculturen





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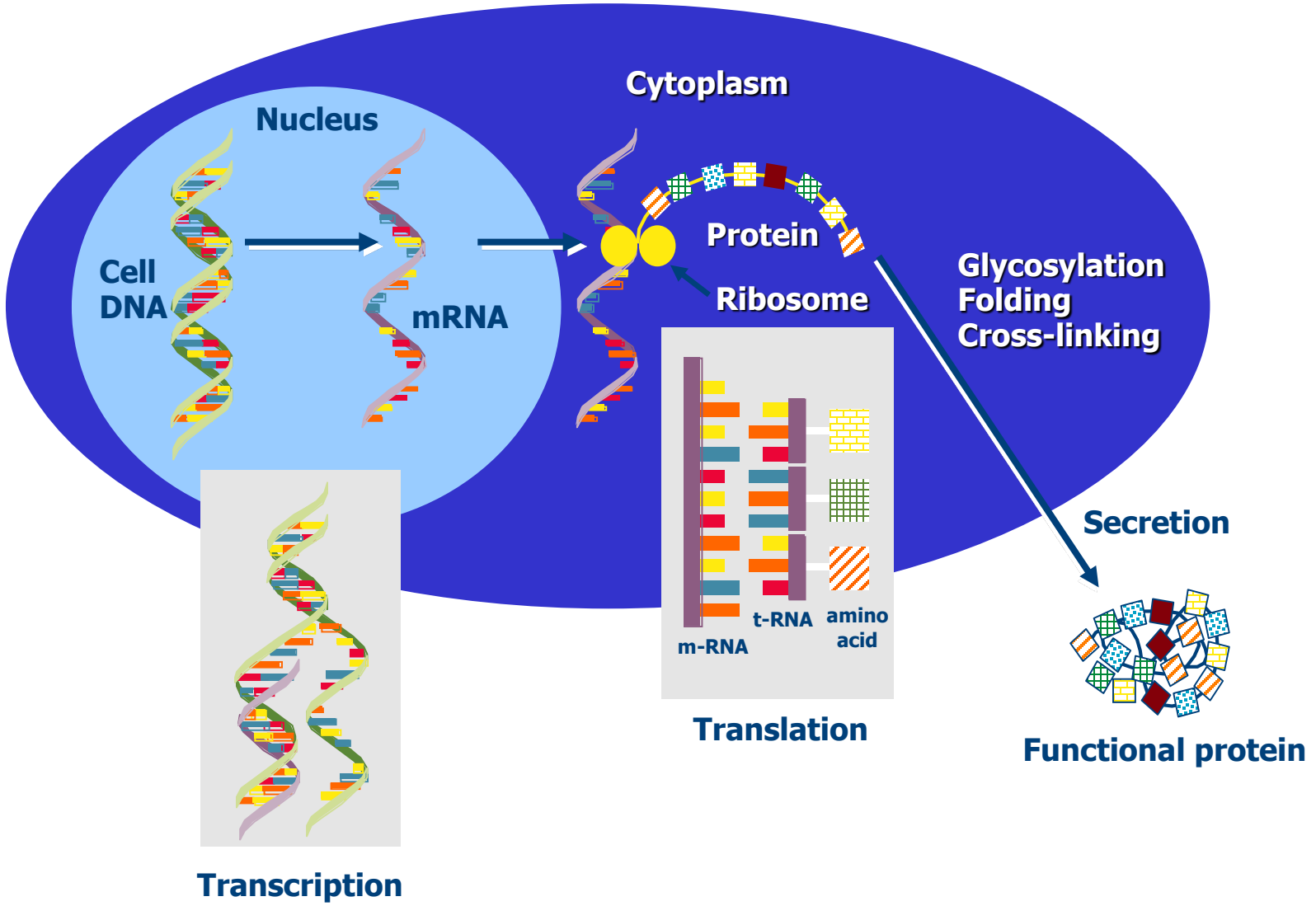
Van DNA tot een functioneel eiwit



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Moleculaire basis van heterogeniteit

- Glycosylering
- Phosphorylering
- Sulfatatie
- Methylering
- N-acylering
- S-Nitrosylatie
- ….
- Cel type en groei omstandigheden

- Deamidatie (bvb. Asn ⟶ Asp)
- Racemizatie (L⟶D)
- Oxidatie (Met, Tyr, His, Trp)
- Disulfide exchange
- …..
- Externe omstandigheden (pH, additieven, temperatuur....)

> 10^8 varianten

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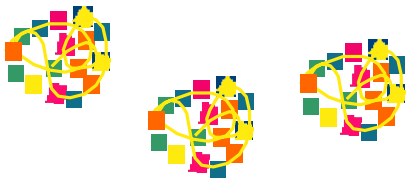
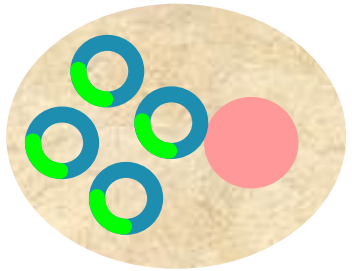
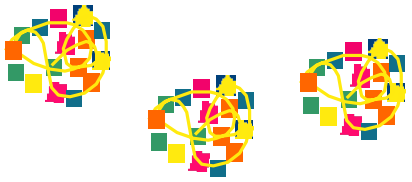
Het proces bepaalt de eigenschappen van het product



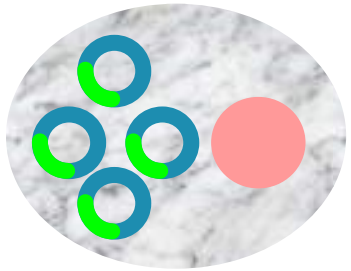
Proteïne



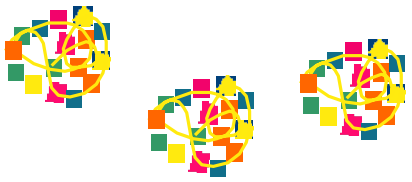
DNA



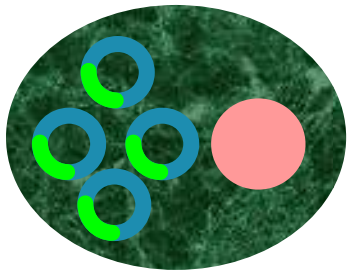
ProTeïnE



DNA



pRotEïNe



DNA

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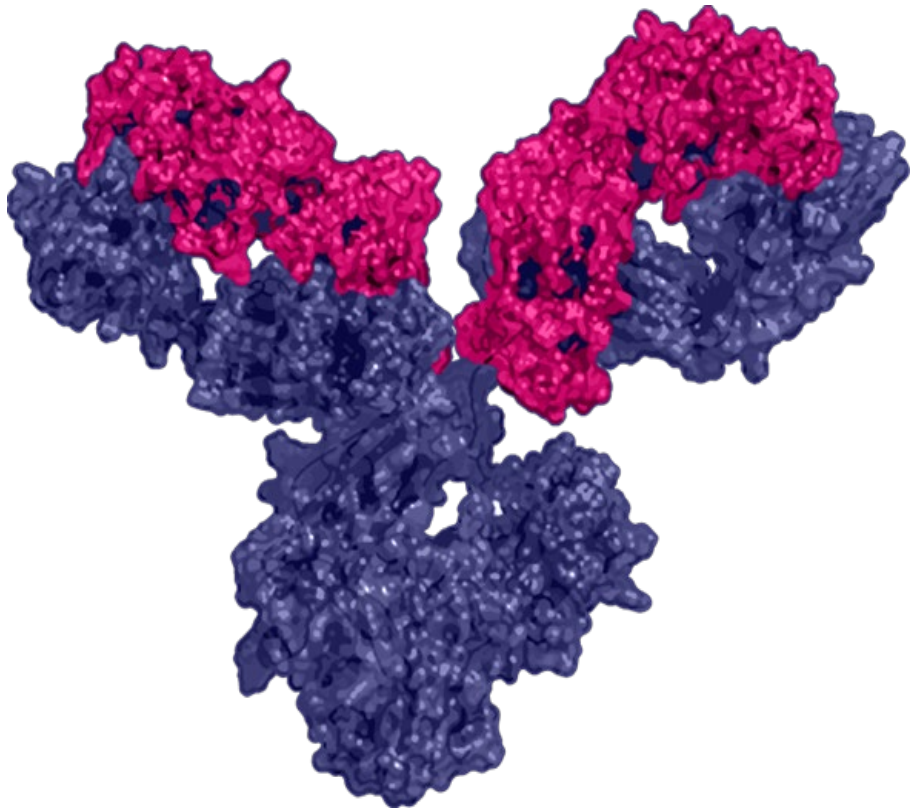
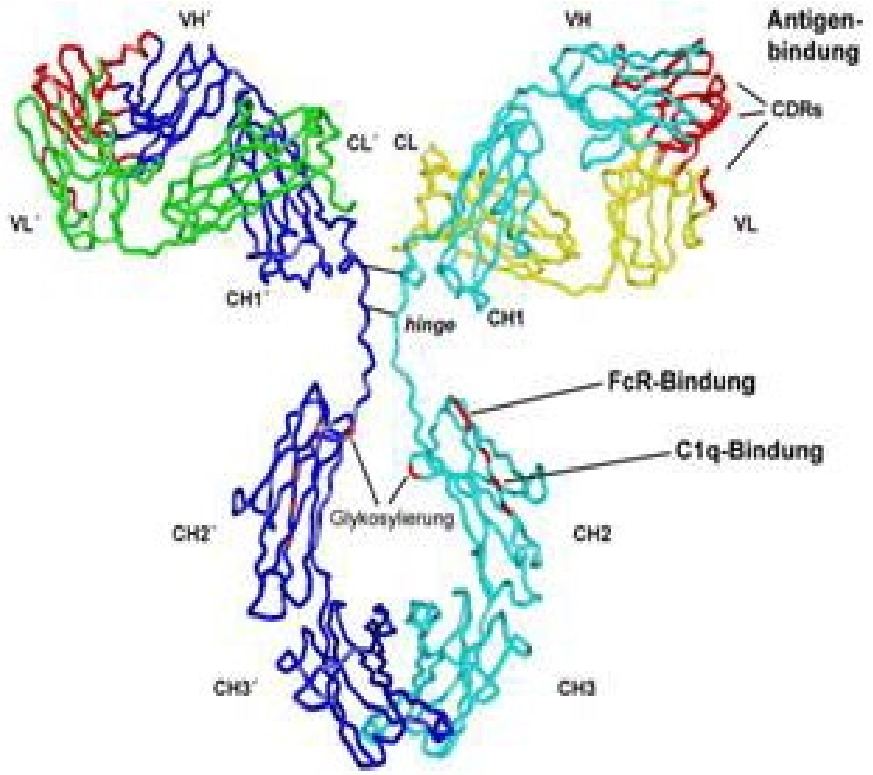
Monoklonaal antilichaam: meerdere functionele domeinen





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Biosimilars

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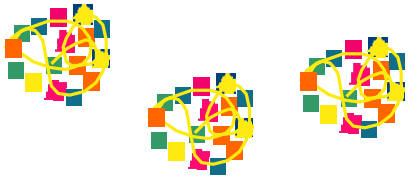
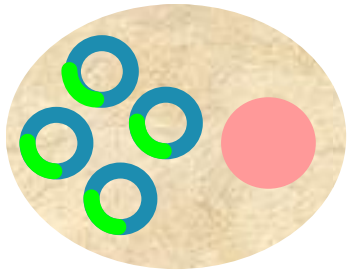
Het proces bepaalt de eigenschappen van het product

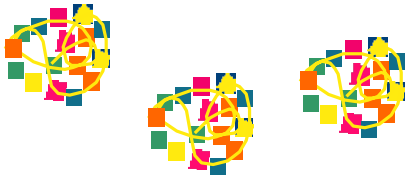


Inflximab, InFlixImab



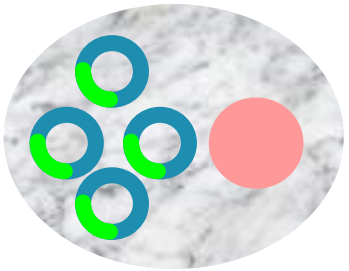


cDNA infliximab

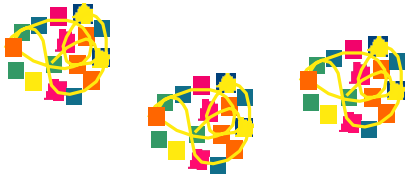


InFlIxImab, inf/IXImaB



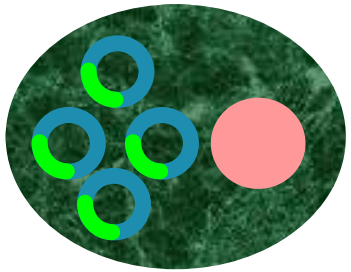


cDNA infliximab



inf/IXiMaB, Inflximab





cDNA inflximab

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European Medicines Agency (EMA)

- Similar biological medicinal product:
  - *"A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the European Economic Area.*
  - *Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established."*

- Guidelines for development and registration since 2006

- EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2014.

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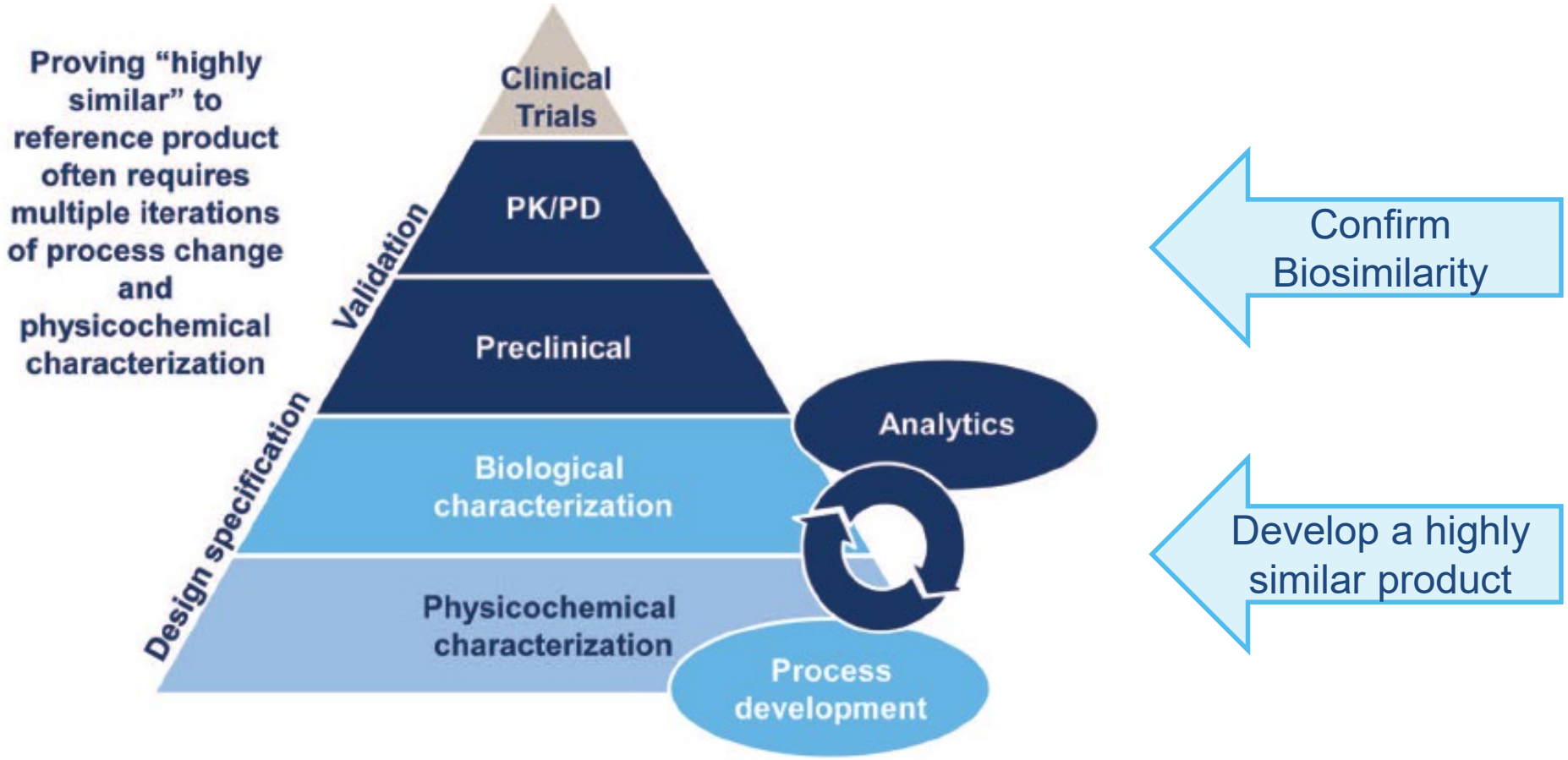
Concept of biosimilar development



McCamish. MAbs. 2011;3(2):209-17

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Registratie vereisten (biosimilar)

Quality

- Drug substance
  - Manufacture
  - Characterisation
  - Control
  - Reference standard
  - Container
  - Stability
- Drug product
  - Description
  - Development
  - Manufacture
  - Control
  - Reference standard
  - Container
  - Stability
- Comparability data
  - Analytical comparison with reference product

Nonclinical

- Pharmacology
  - Primary pharm.
  - Secondary pharm.
  - Safety pharm.
  - Interactions
- Pharmacokinetics
  - ADME
  - Interactions
- Toxicology
  - Single dose
  - Repeat dose
  - Genotoxicity
  - Carcinogenicity
  - Reproduction
  - Local tolerance

Clinical

- Pharmacology
- Pharmacokinetics
  - Single dose
  - Repeat dose
  - Special populations

Study #1

- Efficacy and safety
  - Dose finding
  - Schedule finding
  - Pivotal
    - Indication 1
    - Indication 2
    - Indication 3
    - Indication 4

Study #2

- Post-marketing studies
  - Safety in larger population
  - Efficacy in other indications
  - Immunogenicity

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Registration of Biosimilars: concept of extrapolation

Quality

- Drug substance
  - Manufacture
  - Characterisation
  - Control
  - Reference standard
  - Container
  - Stability
- Drug product
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- Pharmacology
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  - Reproduction
  - Local tolerance

Clinical

- Pharmacology
- Pharmacokinetics
  - Single dose

Study #1

  - Repeat dose
  - Special populations
- Efficacy and safety
  - Dose finding
  - Schedule finding
  - Pivotal
    - Indication 1

Study #2

    - Indication 2
    - Indication 3
    - Indication 4
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  - Safety in larger population
  - Efficacy in other indications
  - Immunogenicity

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Registration of biosimilars (Europe)

- 60 approved in Europa (08/2019)
  - *2 Human growth hormone* (2006)
  - *3 Epoietin alfa* (2007)
  - *2 Epoietin zeta* (2007)
  - *9 Filgrastim* (2008-4, 2009-2, 2010-1, 2013-1, 2014-1)
  - *4 Infliximab* (2013-2, 2016-1, 2018-1)
  - *1 Follitropin alfa* (2013, 2014)
  - *3 Insulin glargine* (2014, 2017, 2018)
  - *2 Etanercept* (2016, 2017)
  - *2 Enoxaparin* (2016)
  - *2 Teriparatide* (2017)
  - *6 Rituximab* (2017)
  - *10 Adalimumab* (2017-4, 2018-4, 2019-2)
  - *1 Insulin Lispro* (2017)
  - *5 Trastuzumab* (2017-1, 2018-4)
  - *2 Bevacizumab* (2018-1, 2019-1)
  - *6 Pegfilgrastim* (2018-5, 2019-1)
  - *1 Pegfilgrastim* (*pending EC decision*)

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How similar are biosimilars ?

Biosimilar ESA (*)

- "Differences were observed at the glycosylation level"
- "Phosphorylated high mannose type structures were detected at higher levels than in Reference ESA"
- "Lower values on N-glycolyl-neuramic acid and diacetylated neuramic acids as compared to Reference ESA"
- "Peptide map showed differences … in O-linked glycan due to a higher sialylation and lower content of the oxidized variant"

Biosimilar hGH (*)

- "The results of this study … demonstrate that Biosimilar rhGH produced at full scale is comparable to Reference Product"
- "The impurity profile of Biosimilar hGH shares some similarity with Reference hGH; however the profiles are not identical"
- " … impurities, … , are present in the Biosimilar hGH batches and are not in any Reference hGH batches"
- "Additionally, there appears to be a higher level of deamidated variants in the Biosimilar hGH samples"

Biosimilar IFX (*)

- "….. all major physicochemical characteristics and biological activities of biosimilar IFX were comparable to those of the reference product"
- "….difference in the amount of afucosylated infliximab, translating into a lower binding affinity towards FcγRIIIa receptors and a lower *ex vivo* antibody-dependent cellular cytotoxicity (ADCC) activity…."
- "… less intact IgG …. , mainly due to a higher proportion of non-assembled form. …. unlikely to impact its biological activity"
- "a higher level of C-terminal lysine variability"
- "…slightly higher level of aggregates …"

Biosimilars are Similar, not identical

(*) Based upon European Public Assessment Report on respective biosimilars

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Interchangeability

EMA

- Only evaluation of biosimilarity, no recommendation on interchangeability
- No guidance
- Currently, designation of interchangeability is delegated to national competent authorities

US-FDA

- Two-step process
  1. Biosimilarity
  2. Interchangeability
- Guidance (5/2019)
- Implication: Interchangeability designation by FDA allows automatic substitution provided that state legislature permits such substitution

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Biosimilarity ≠ Interchangeability

- Not identical to reference
- Claim for interchangeability needs to be proven (in both directions!) and holds only for the two products evaluated
- Divergence over time
- Two or more biosimilars from the same reference product have not been compared to each other.

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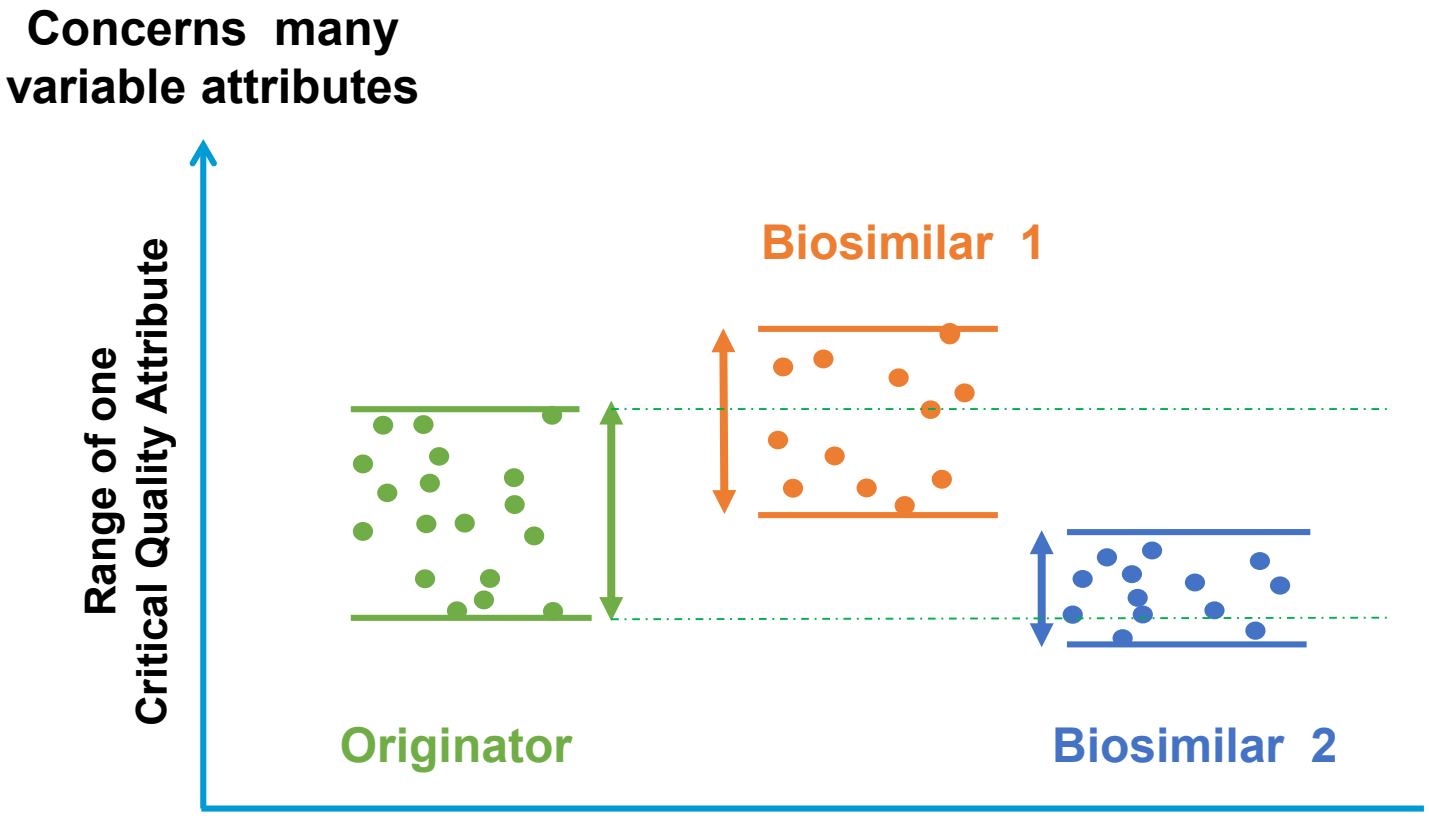
Variability in biologicals (including biosimilars)– Acceptable, established margins



- Adapted from Gonçalves J, *et al. Clin Exp Rheumatol* 2016;34(4):698-705.

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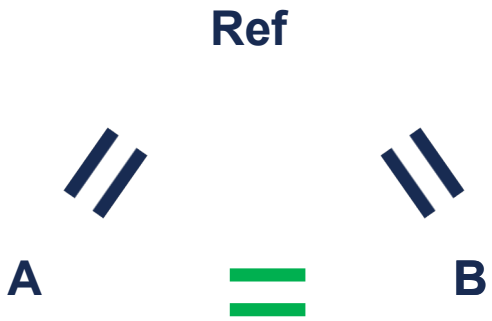
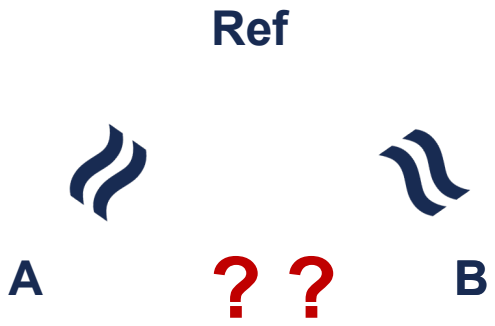
Chemisch geneesmiddel

generiek A en B



Biologisch geneesmiddel

biosimilar A en B



Biosimilariteit is niet automatisch gelijk aan uitwisselbaarheid

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Switchen in de praktijk: implicaties

- Indien een patient geswitcht wordt, is een verhoogde waakzaamheid aanbevolen

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Home / Biosimilars / General / British diabetologists issues position statement on biosimilar insulin

British diabetologists issues position statement on biosimilar insulin

Posted 14/12/2018

The Association of British Clinical Diabetologists (ABCD) has issued a position statement on the use of biosimilar insulin. The statement summarises information on the advantages and disadvantages of using biosimilar insulins and gives the association's position on when



British diabetologists issues position statement on biosimilar insulin

The Association of British Clinical Diabetologists (ABCD) has issued a position statement on the use of biosimilar insulin. The statement summarises information on the advantages and disadvantages of using biosimilar insulins and gives the association's position on when biosimilar insulins be used [1].



medicines!
e-mail
SUBMIT
Biosimilars

The association's position on biosimilar insulins is therefore that:

1. Biosimilar insulins could be considered for all newly diagnosed patients with type 1 diabetes who have not been exposed to the reference drug and in patients who require a review of their therapy due to poor control.
2. When patients are established on a current insulin regimen, those achieving their target HbA1c without hypoglycaemia should not be automatically switched to a biosimilar insulin.
3. Following the switch to a biosimilar insulin, it is recommended that provision for review and ongoing supervision by a specialist team is provided.

The ABCD concludes that 'with the advent of an increasingly complex portfolio of insulin therapy, it is imperative that all healthcare staff receive education about safe insulin prescribing which specifically includes information on biosimilar insulin'.

Switchen in de praktijk: implicaties

- Indien een patient geswitcht wordt, is een verhoogde waakzaamheid aanbevolen
- Geen enkele informatie beschikbaar met betrekking tot switchen tussen verschillende biosimilars!
- De gerandomiseerde betrouwbare switch studies hebben tot nog toe geen majeure problemen aangetoond, maar:
  - Het aantal studies is relatief beperkt
  - Studies met één biosimilar leren niets over een andere biosimilar
  - Het (heen en weer) switchen wordt op basis van het 'voorzichtigheidsprincipe' afgeraden
  - Traceerbaarheid dient ten allen tijde gewaarborgd te worden

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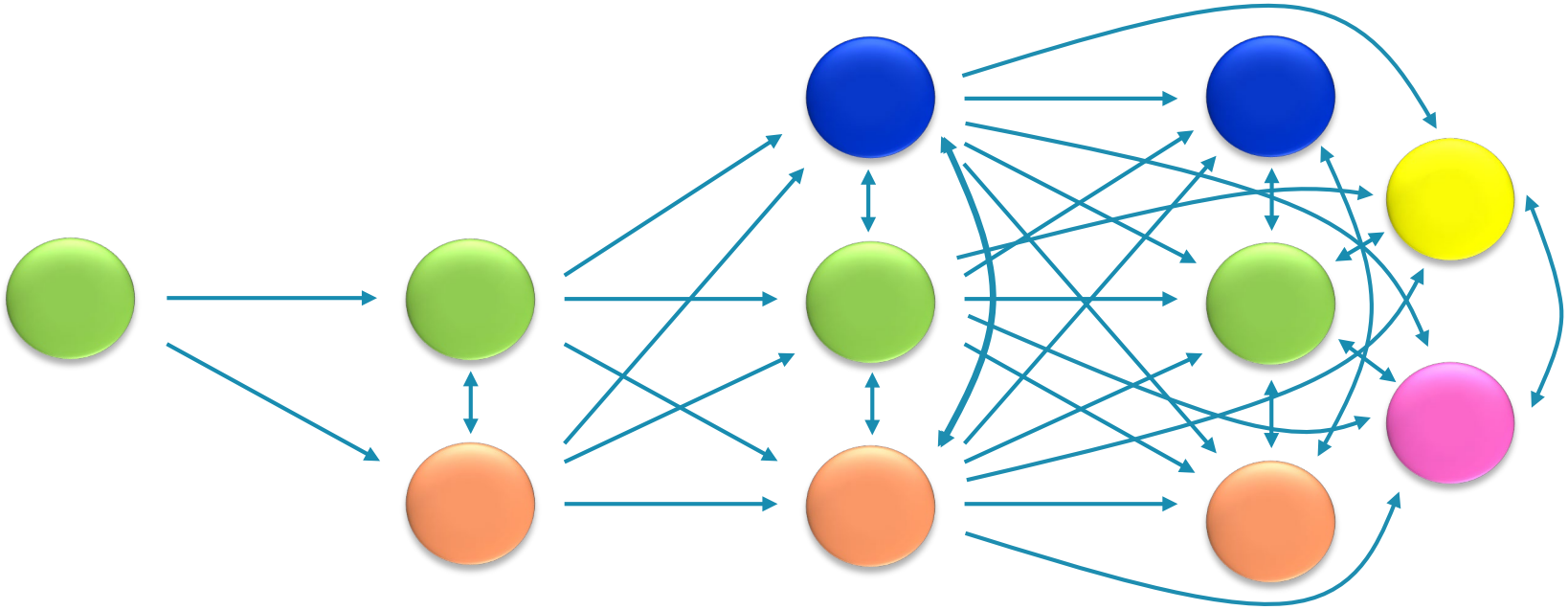
Multiple Switches Between Biosimilars from the Same Reference

Originator biologic → One biosimilar → Two biosimilars → Four biosimilars



Biosimilars of originator R

originator R

biosimilar B1

biosimilar B2

biosimilar B3

biosimilar B4

Take-home message

- De kwaliteit van een goedgekeurde biosimilar is, zoals bij ieder geregistreerd geneesmiddel, steeds gewaarborgd
- Voorschrijven van biologicals (incl. biosimilars): op merknaam (no VOS)
- Stimuleren van gebruik van biosimilars gebeurt bij voorkeur bij ‘bio-naïeve’ patiënten
- Probeer switchen te vermijden (product afhankelijk)
- Indien switch, vermijd zeker veelvuldig switchen
- Een immunologische response (= nevenwerking) op een biologisch geneesmiddel treedt op met vertraging

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