



INTERNATIONAL GENERIC PHARMACEUTICAL ALLIANCE

IGPA's view on implementation of the WHO guidelines on Similar Biotherapeutic Products (SBPs)

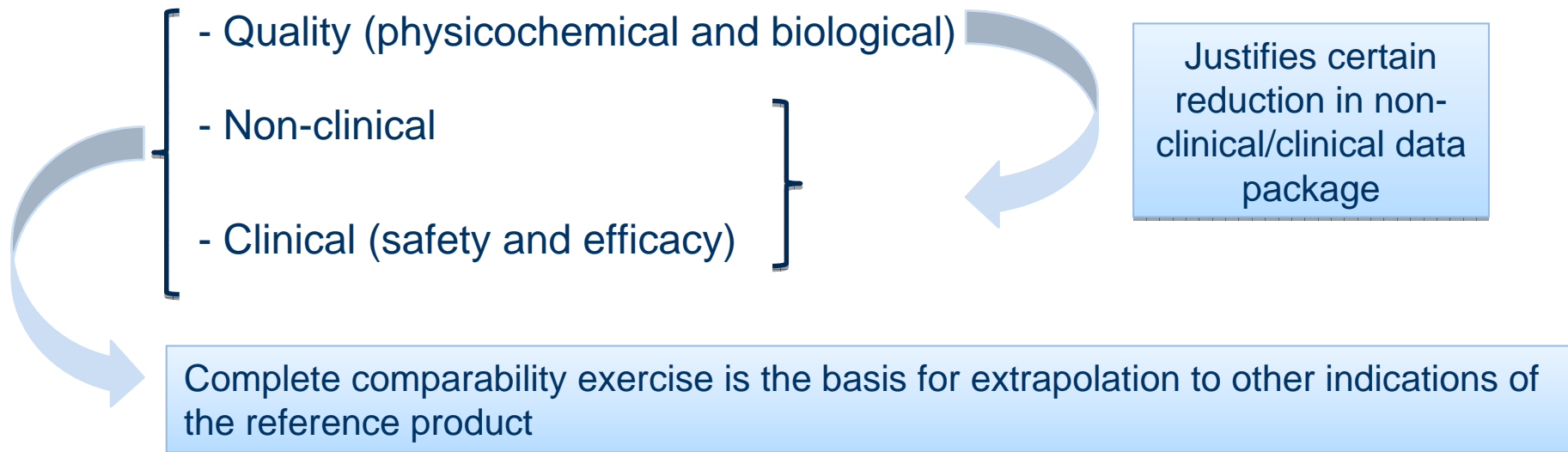
Martin Schiestl
Scientific and Regulatory Advisor
Sandoz Biopharmaceuticals

WHO/KFDA Workshop on implementing
WHO guidelines on evaluating similar biotherapeutic products
Seoul, 24 – 26 August 2010

All trademarks used for this presentation are the property of the respective owners

What does WHO guideline provide for?

- Comparability concept for a Biosimilar/SBP
 - Complete stand alone manufacturing process development
 - Demonstrated comparability at following levels



- Defines, what is a Biosimilar/SBP and what is a new biologic entity (although the designed amino acid sequence might be the same as that of an originator)

SBPs Guidelines

- The key concepts of the WHO guidelines are essentially the same as existing and recently developed regional guidelines in
 - European Union (also implemented in Australia and Switzerland)
 - Japan, Canada, Republic of Korea, Malaysia, Singapore
- Upcoming guidelines may benefit from the WHO guidelines and the discussions that lead to the final text in
 - Brazil, Mexico, South Africa

Considerations for implementation of WHO Guidelines

-|

- WHO guidelines are quite detailed in certain sections, e.g. statistical considerations for clinical studies
- Level of detail is helpful and applicable for most situations, however it should be noted that based on scientific rationale, alternative solutions might be possible
- As manufacturing processes are changed over time with originator molecules, use prior experiences in judging such changes for approval.
 - E.g. comparability exercises have been used for years to evaluate whether a process change that changes the molecule should be approved. Such comparability exercises provide data and experience for direct application to biosimilar development and approval
- Newer analytical technologies provide robust characterization throughout the life cycle of a product

Considerations for implementation of WHO Guidelines

-II

- The non-clinical section may be interpreted **ambiguously** with regard to the amount of required non-clinical studies
- First part contains **many factors** that may elicit need for additional non-clinical studies, like
 - Significant differences to reference product in cell expression system or in the purification methods, (this is always the case for a Biosimilar/SBP)
 - Drug substance difficult to characterize or has narrow therapeutic index
 - ↳ May lead to expectation to perform extensive non-clinical program
- Last paragraph describes that based on **demonstrated similarity** of the quality between SBP and the Reference Biotherapeutic Product (RBP), studies for safety pharmacology, repro tox, genotoxicity, carcinogenicity are generally not required
 - ↳ The minimal non-clinical program described in the same section is sufficient if similarity on the quality level can be shown (which would be also the same interpretation as provided e.g. by the EU guidelines)

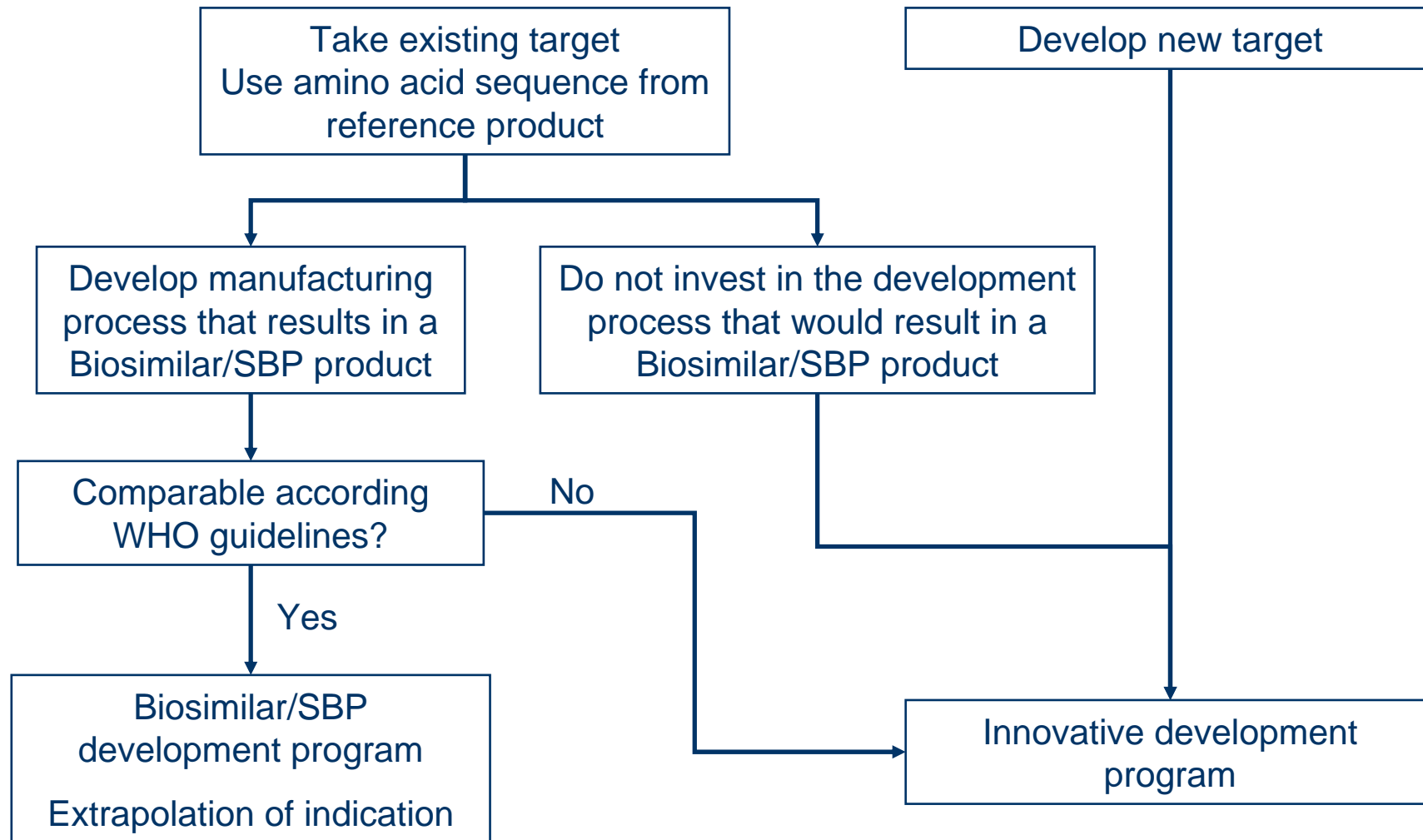


What is not regulated by WHO guidelines according to introduction section

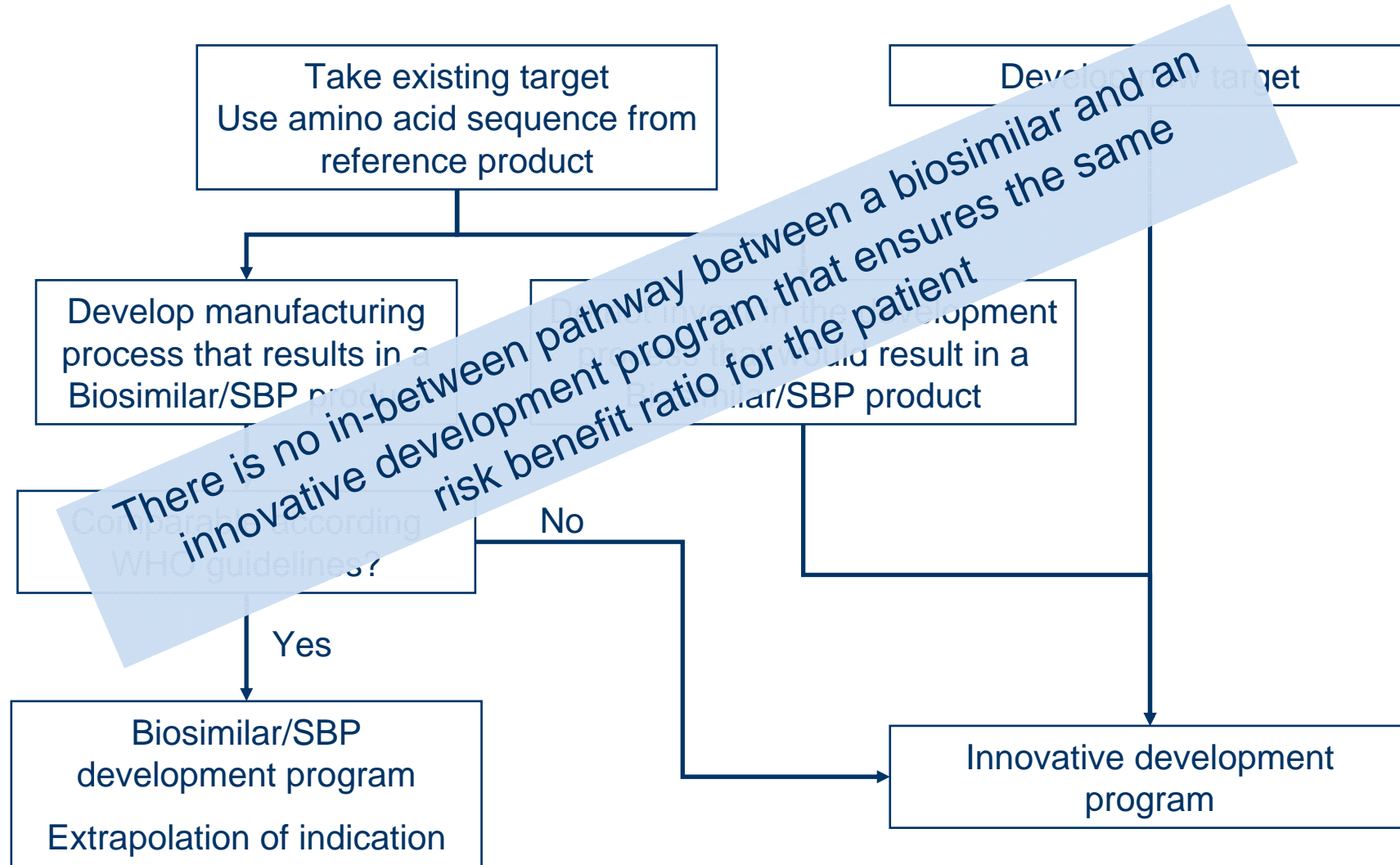
- Intellectual property issues
- Interchangeability and substitution
- Labelling and prescribing information

- WHO: “... need to be defined by the national authority”
- Regulatory assessments should not be linked with patent resolution process
↳ otherwise this may lead to delays of Biosimilar approval by formal hurdles
- Interchangeability and substitution: Scientific concepts are evolving – also consider that substantial changes in originator products occur without requirement for switching studies
- Labelling and prescribing information: WHO guidelines contain a short section on this topic, which provides a good basis for national authorities

Interpretation of WHO guidelines: Options for a biopharmaceutical company



Interpretation of WHO guidelines: Options for a biopharmaceutical company



Only biologics that comply with WHO guidelines should be designated “Biosimilars/SBPs”

Different process = different product

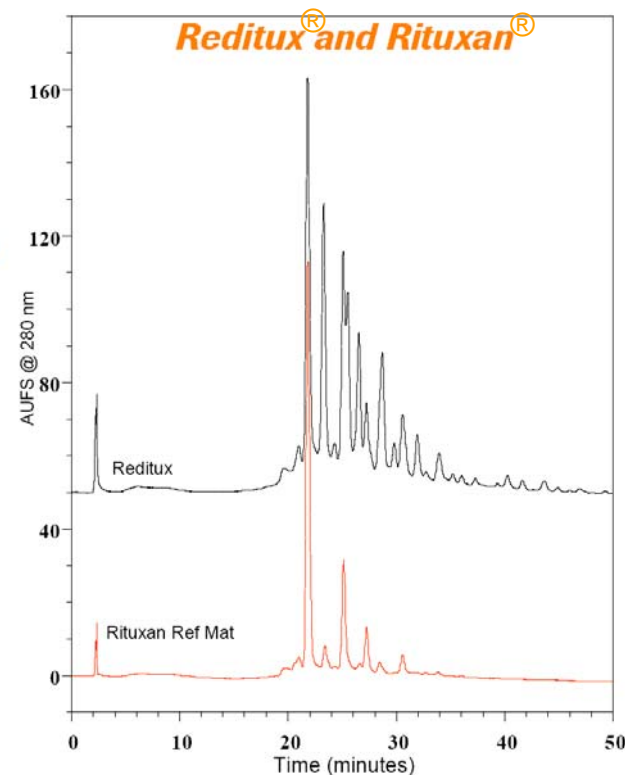
Exhibited differences when compared to branded product

- Same amino acid sequence
- Host cell protein content much higher
- Content of aggregates not comparable
- Glycosylation not comparable
- Effector function not comparable
- Charge distribution not comparable
- Clinical (PK/PD) published data - 17 patients



Different manufacturing means:

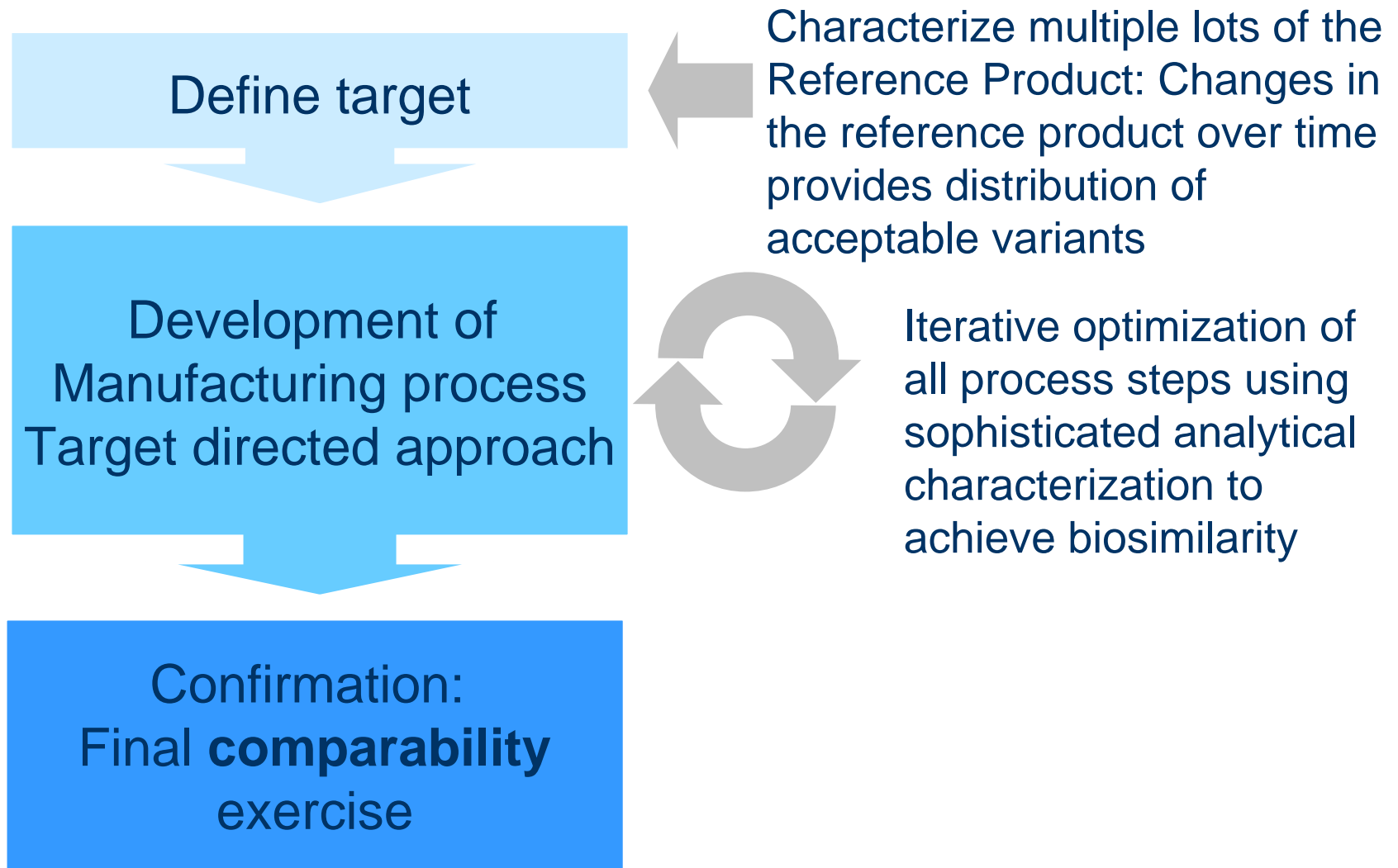
- Different drug
- Different safety/efficacy profile?



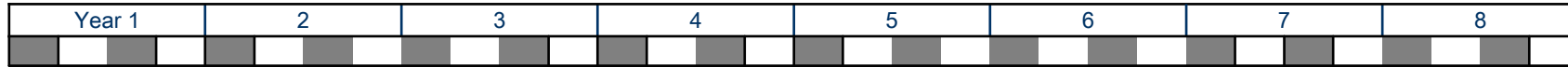
Comparison by Cation Exchange Chromatography

Source: Mike Doherty, Global Head Regulatory Affairs, Roche Pharmaceuticals, at Roche Investor Day 2010, March 18, 2010, see http://www.roche.com/investors/ir_agenda/rid_2010.htm?track=8 and www.roche.com/irp100318_md.pdf

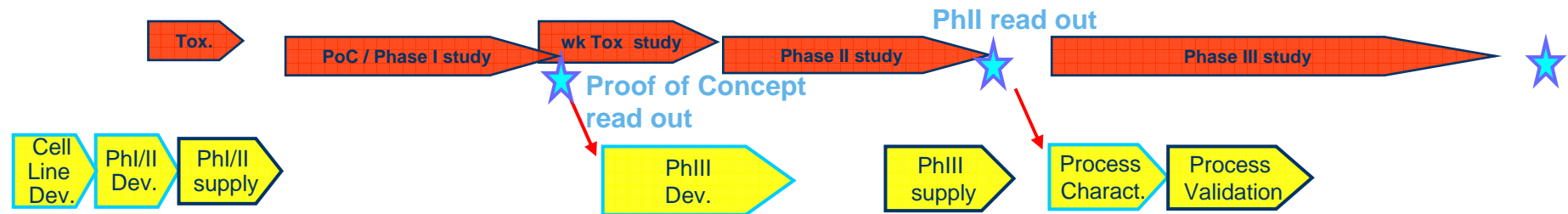
Approvable “Biosimilars/SBPs” are systematically engineered to match the reference product



What is the difference between innovative and Biosimilar/SBP development?



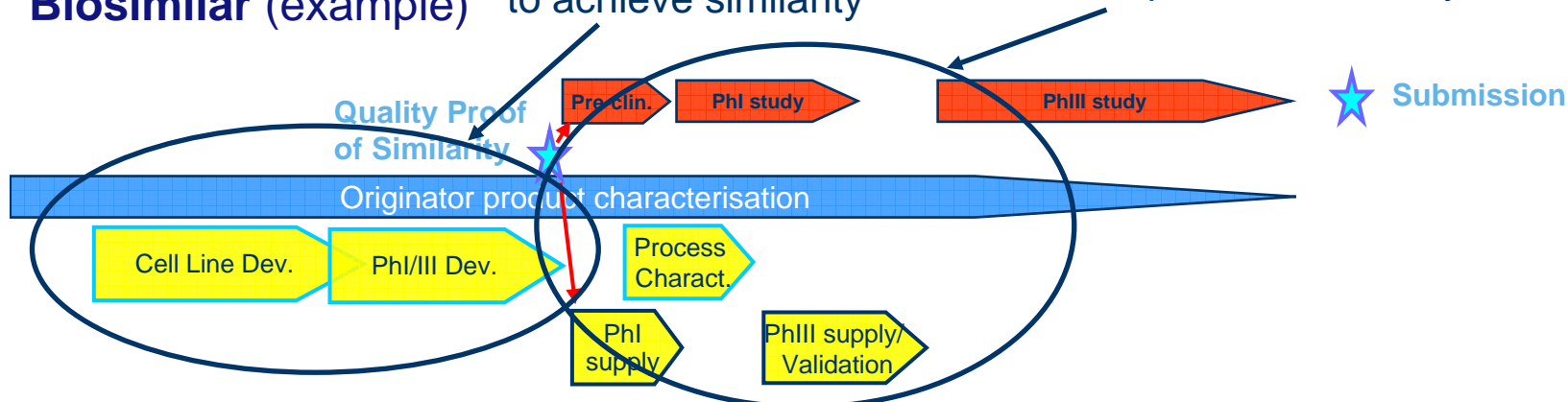
Innovative biopharmaceutical (example)



Longer manufacturing process development to achieve similarity

Shorter preclinical and clinical development if similarity is achieved

Biosimilar (example)



Current experience with Biosimilars/SBPs

- Non glycosylated proteins
 - Somatropin
 - Filgrastim
- Complex glycosylated proteins
 - Erythropoietin
- Currently in development
 - Monoclonal antibodies
 - others

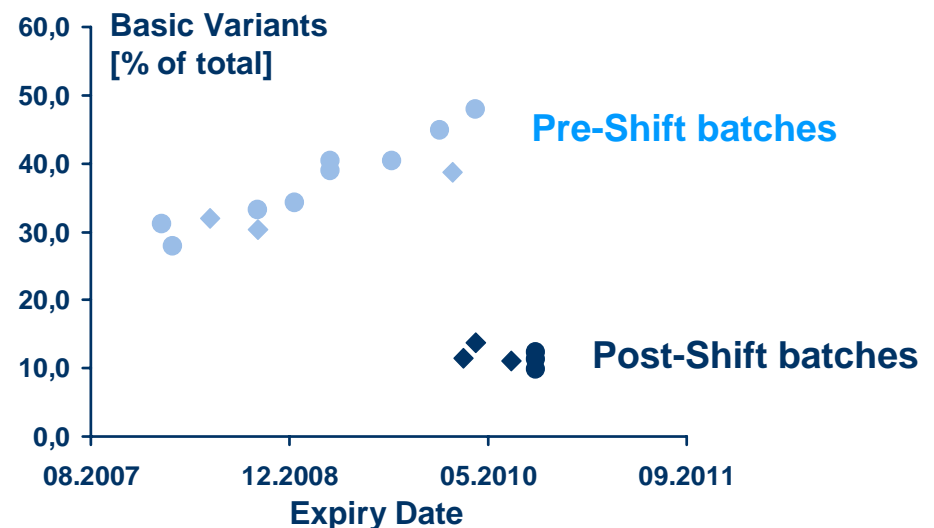
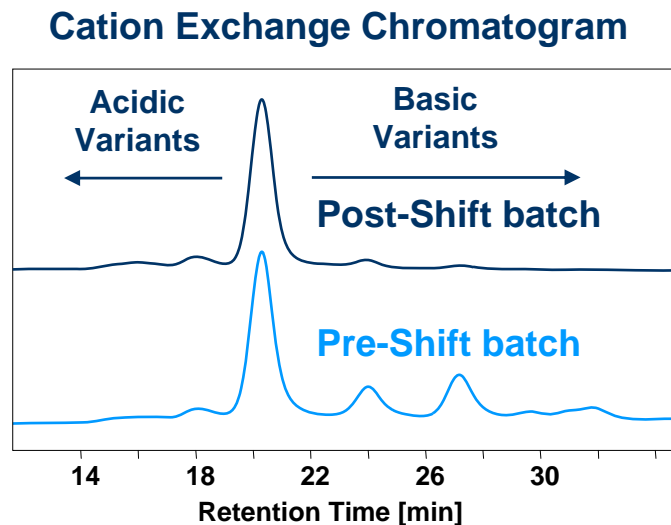
How difficult is it to make a Biosimilar/SBP?

- Technologies have advanced to an extent **enabling any state of the art company to perform a Biosimilar/SBP development**
- Industry and regulators have experience in managing major manufacturing changes in originator molecules using a comparability exercise similar to approval of Biosimilars/SBPs
- The closer the Biosimilar/SBP is to the originator using sophisticated analytical techniques, the more confident one can be extrapolating to the originator. Since originators change their molecules by process changes over time, if the biosimilar quality is within the range of the old and new originator molecule, extrapolation is warranted as in comparability exercises

Originators may exhibit changes in quality attributes

Example A: Monitoring batches of MabThera®/Rituxan® (rituximab):

➔ Shift in the identity profile measured by cation exchange chromatography

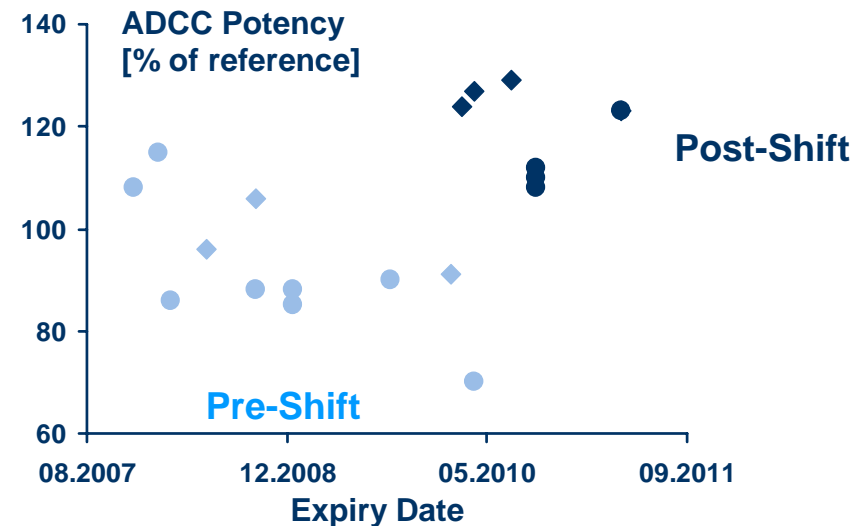
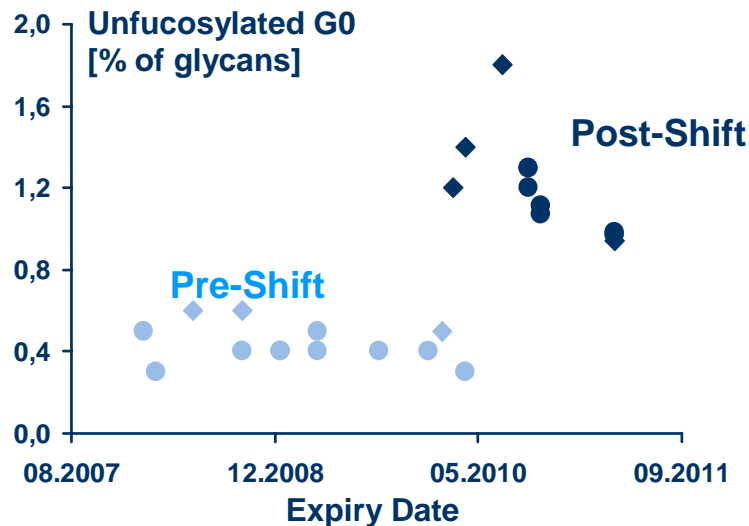


- Separation of differently charged variants, e.g. basic N-terminal glutamine and C-terminal lysine variants
- Indication of a change in the manufacturing process?

Originators may exhibit changes in quality attributes

Example B: Monitoring batches of MabThera® /Rituxan® (rituximab):

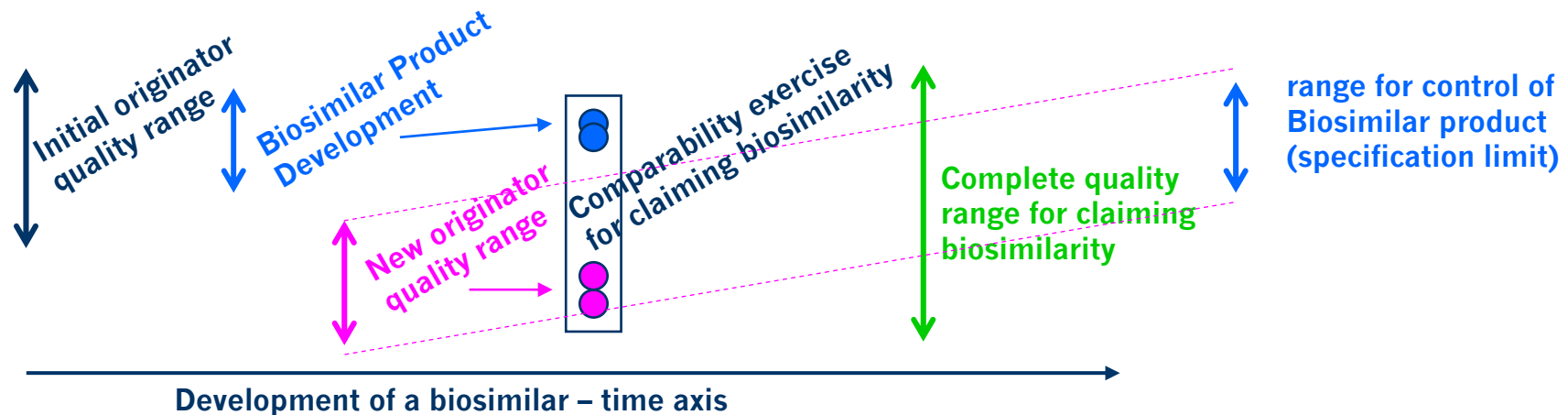
➔ Shift in glycosylation profile and ADCC potency



- Differences/shift in glycosylation pattern results in different potency in cell-based assays
- Product label remained unchanged – indicating comparable quality

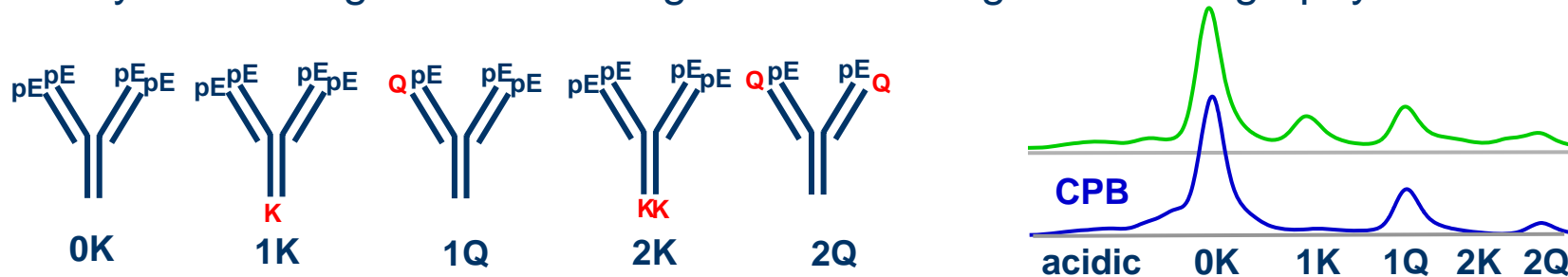
What if originator changes quality attributes? e.g. due to process manufacturing changes

- Manufacturing process changes are tightly regulated (see ICH Q5E)
 - Change of quality attributes only acceptable if they do not alter safety/efficacy
- ➔ For demonstrating biosimilarity it is therefore acceptable to use the upper and the lower limit of the pre and post shift material
- ➔ However, the Biosimilar/SBP release specification should be as tight as the current originator specification but need not to be the same values

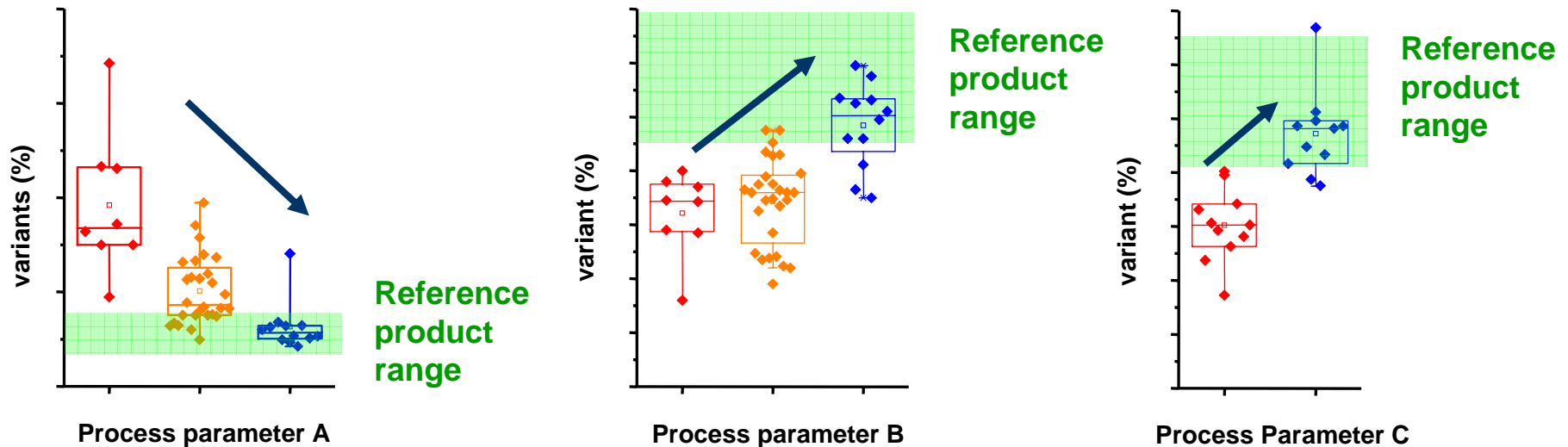


Examples of iterative biosimilar development: A. Making mAb charge variants biosimilar

Analysis of charge variants using cation exchange chromatography



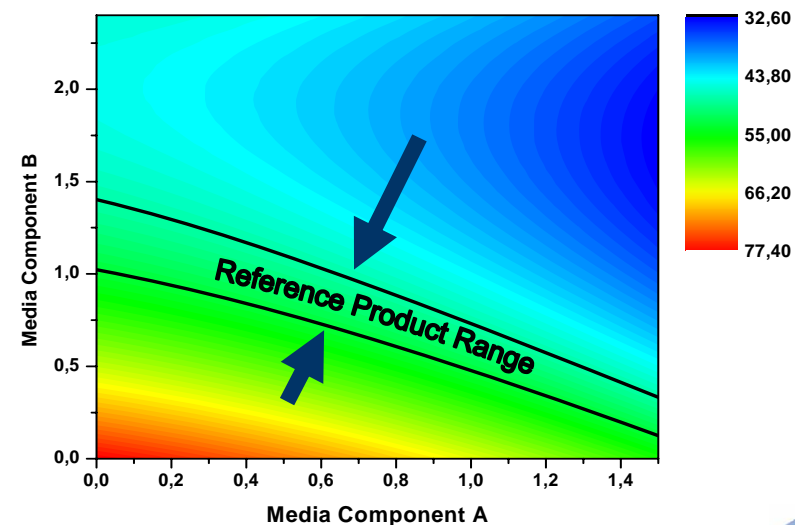
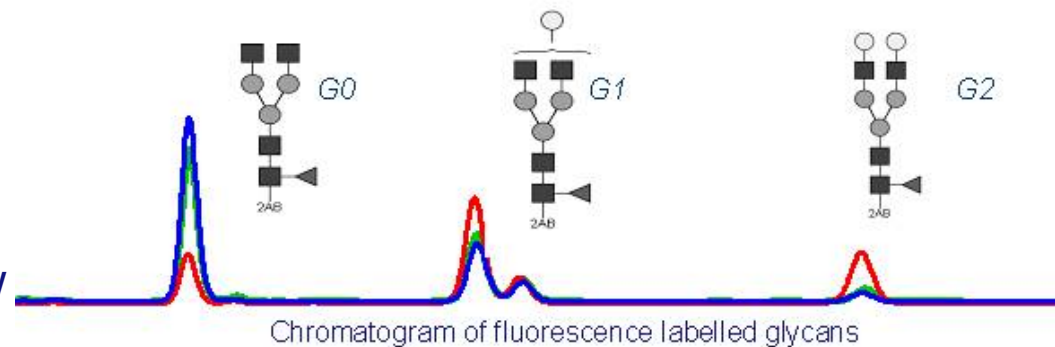
Targeting charge-variants via bioreactor process parameters



Examples of iterative biosimilar development: B. Making the glycosylation comparable

Targeting galactosylation of mAb by cell culture process media optimization

- Specific media components consistently result in desired galactosylation state in dose-dependent manner
- Other media components allow targeting of fucosylation or mannosylation



How to select a reference product for global development programs?

- WHO guideline recognizes the issue:
 - WHO: “NRA’s may need to consider establishing additional criteria to guide the acceptability of using a RBP licensed or resourced in other countries”
- This option is important because
 - The innovator product is normally based on one single development
 - Scientifically no need to perform the comparability exercise for every country/region
 - Performing comparability for every country is ethical questionable and will increase the development costs → limited cost reduction for health care systems
- One comprehensive comparability package performed should be sufficient for the submission and licensure of SBPs worldwide
 - Against a reference product authorized by a stringent authority
 - According to the high comparability requirements laid down in the WHO guidelines

Conclusion

- WHO guidelines on evaluation of SBPs is an important step forward in the standardization of the licensing procedures for Biosimilars/SBPs
- Provides clear advice for biosimilar industry to make Biosimilars/SBPs with the same risk/benefit ratio as the reference products
- WHO guidelines contain the same key concepts as already laid down in a number of existing regional guidelines (e.g. EU, JP, Can) and may help optimize and harmonize guidelines currently being developed by many countries and currently in a draft status
- One comprehensive comparability package performed against a reference product authorized in a highly-regulated market should be sufficient for all regions
- Changes in the reference product over time offers a distribution of product attributes that can be used by regulators to judge similarity and extrapolation for safety and efficacy just as in a comparability exercise following a manufacturing process change