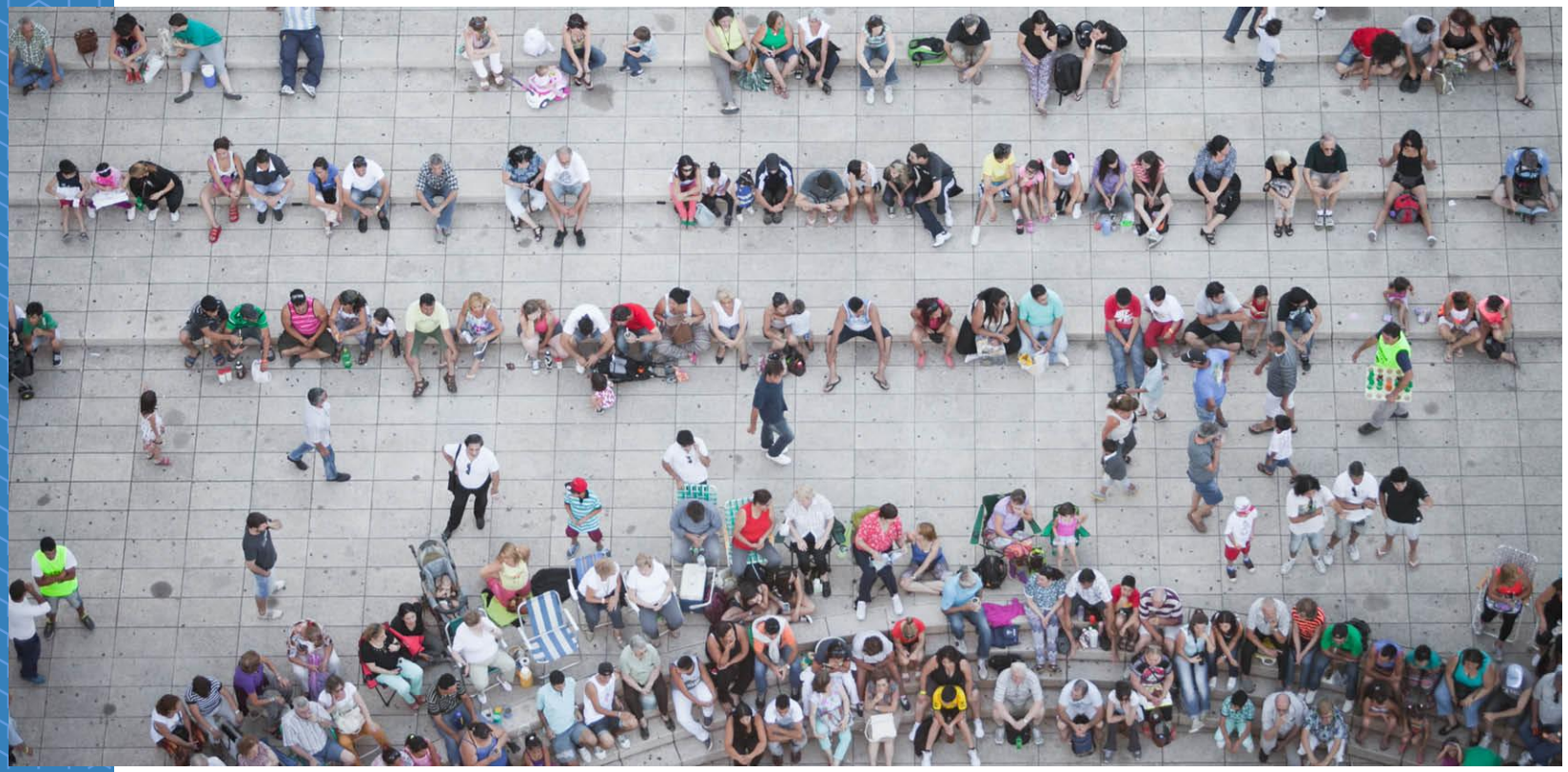
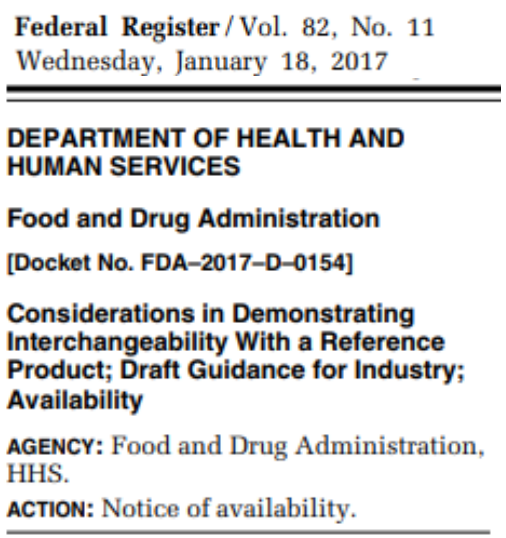


# Control of variability to ensure a clinically consistent product

**Hillel P. Cohen PhD, Executive Director of Scientific Affairs**
**Sandoz Inc.**
**GRx-Biosims 2018 meeting**
**September 6, 2018**

SANDOZ A Novartis Division

# Variability due to manufacturing process changes may be of regulatory concern for biosimilars and interchangeable biologics



Federal Register / Vol. 82, No. 11
Wednesday, January 18, 2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2017–D–0154]

Considerations in Demonstrating Interchangeability With a Reference Product; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

**BIOSIMILAR BIOLOGICAL PRODUCT REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022**

**II. ADVANCING DEVELOPMENT OF BIOSIMILAR BIOLOGICAL PRODUCTS THROUGH FURTHER CLARIFICATION OF THE 351(k) REGULATORY PATHWAY**

**C. On or before March 31, 2019, FDA will publish draft guidance describing processes and further considerations related to post-approval manufacturing changes for biosimilar biological products.** FDA will work toward the goal of publishing a revised draft or final guidance within 18 months after the close of the public comment period.

Since the mid-1990s, FDA has approved manufacturing changes for biological products based on data from comparability assessments comparing the pre-change and post-change product using comparative analytical, and, when necessary, animal and/or clinical (*e.g.,* pharmacokinetic, immunogenicity) studies. **A demonstration of comparability between pre- and post-change product supports a determination that the safety and efficacy profile remains the same for the product. With respect to interchangeable products, are there considerations in addition to comparability assessments that FDA should consider in regulating post-approval manufacturing changes of interchangeable products?**

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# Comments from a few companies to the FDA

Periodic reassessment of interchangeability:

"Interchangeability may be threatened not only by manufacturing changes implemented for the biosimilar, but also by changes implemented for the reference product, and by drift of either product over time. Hence, ***the sponsor of the biosimilar product should be expected periodically (such as no later than every 2 or 3 years after the previous such assessment) to reassess interchangeability***." [1]

Clinical bridging studies after every manufacturing process change:

"To address the potential for product drift between the reference product and an interchangeable biological product, a three-way bridging study should be conducted using ICH Q5e as the framework for analytical and functional comparison. The three way bridging study should be conducted between the current reference product, the pre-change interchangeable biological product and the post-change interchangeable product. In addition, ***there should be a three way bridging clinical PK and PD (if available) for all three products***." [2]

Comment from Johnson and Johnson to Docket FDA-2017-0154-0042 (accessed 23 Aug 2018)
Comment from Genentech to Docket FDA-2017-0154-0042 (accessed 23 Aug 2018)

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3

# Can variability in quality attributes over time cause clinical differences?





SANDOZ A Novartis Division

EXPERT OPINION ON BIOLOGICAL THERAPY, 2018
VOL. 18, NO. 4, 369–379
https://doi.org/10.1080/14712598.2018.1421169

Taylor & Francis
Taylor & Francis Group

REVIEW



# Maintaining consistent quality and clinical performance of biopharmaceuticals

William C. Lamanna[a], Johann Holzmann[b], Hillel P. Cohen[c], Xinghua Guo[b], Monika Schweigler[b], Thomas Stangler[b], Andreas Seidl[d] and Martin Schiestl[a]

[a]Sandoz Biopharmaceuticals, Sandoz GmbH, Kundl, Austria; [b]Technical Development Biosimilars, Biologics Technical Development and Manufacturing, Novartis, Sandoz GmbH, Kundl, Austria; [c]Scientific Affairs, Sandoz Inc, Princeton, NJ, USA; [d]Technical Development Biosimilars, Biologics Technical Development and Manufacturing, Novartis, Hexal AG, Oberhaching, Germany

**ABSTRACT**

**Introduction**: Biopharmaceuticals are large protein based drugs which are heterogeneous by nature due to post translational modifications resulting from cellular production, processing and storage. Changes in the abundance of different variants over time are inherent to biopharmaceuticals due to their sensitivity to subtle process differences and the necessity for regular manufacturing changes. Product variability must thus be carefully controlled to ensure that it does not result in changes in safety or efficacy.

**Areas covered**: The focus of this manuscript is to provide improved understanding of the science and strategies used to maintain the quality and clinical performance of biopharmaceuticals, including biosimilars, throughout their lifecycle. This review summarizes rare historical instances where clinically relevant changes have occurred, defined here as clinical drift, and discusses modern tools used to prevent such changes, including improved analytics, quality systems and regulatory frameworks.

**Expert opinion**: Despite their size complexity and heterogeneity, modern analytics, manufacturing quality systems and comparability requirements for the evaluation of manufacturing changes cumulatively help to ensure the consistent quality and clinical performance of biopharmaceuticals throughout their product lifecycle. Physicians and patients can expect the same safety and efficacy from biopharmaceuticals and their respective biosimilars irrespective of batch or production history.

**ARTICLE HISTORY**
Received 18 September 2017
Accepted 20 December 2017

**KEYWORDS**
Biopharmaceutical; biosimilar; consistency; drift; equivalence; manufacturing

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# Agenda

- What & why of variability
  - Normal variability, deviations, drift & shift
  - Divergence is not a concern for properly controlled biosimilars
  - Variability in some reference biologics has already been documented
- How to control – tools and concepts
  - Quality system & GMP
  - Specifications
  - Reference standards
  - Comparability
  - Analytical technology
  - QbD & Process Design
  - Continued Process Verification

GMP, good manufacturing practices; QbD, quality by design

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GMP, good manufacturing practices; QbD, quality by design

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# Causes of variability

- Normal variability (within batch, or batch-to-batch)
  - all manufacturing processes have inherent variability
  - biologics are particularily sensitive to variability in the process parameters and materials
  - common cause variation – the natural pattern / noise in the system
- Process deviations
  - unintended, unanticipated and isolated events
  - special cause variation – unnatural pattern / signal within the system
  - root cause identification and CAPA

CAPA, corrective and preventive action

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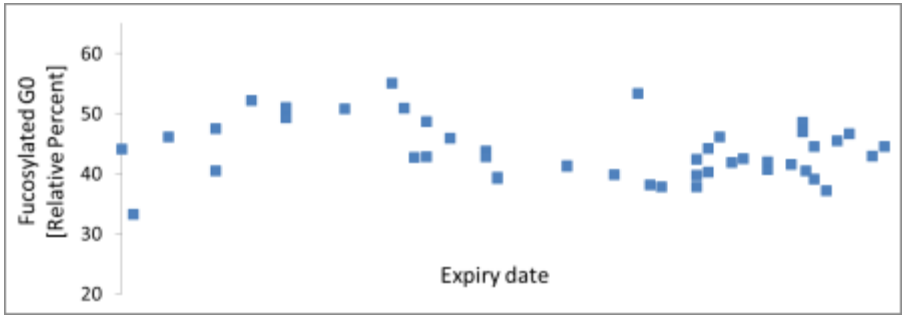
# Variability is inherent in biologics

## Batch-to-batch

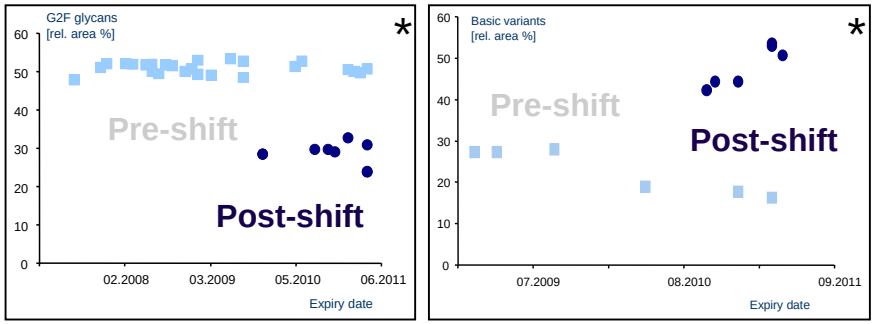
- Non-identicality is a normal principle in biologics
- No batch of any biologic is “identical” to the other batches
- Variability is natural even in the human body and usually not problematic

**Variability of major glycan variant in commercial mAB**




## Manufacturing changes

- Manufacturing changes occur due to process improvements, scale up, etc
- Differences in attributes sometimes significantly larger than batch-to-batch variability




* M. Schiestl et al. Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceutical; Nature Biotechnology (2011) 29:310

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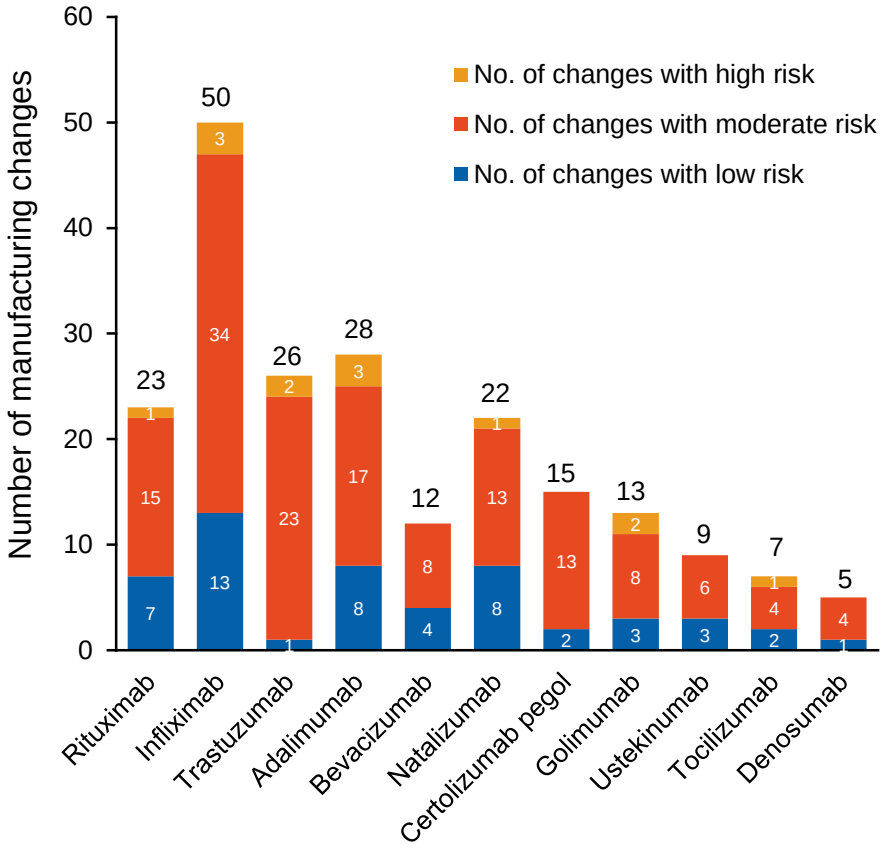
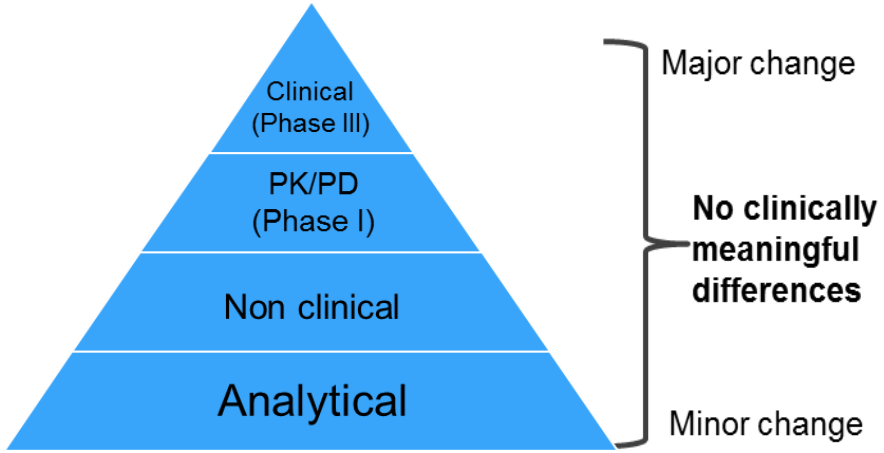
# Biologics may change their manufacturing processes multiple times, which can impact analytical variability

~400 process changes for 29 mAbs/fusion proteins in the EU (~5% high risk changes)




Process changes can result in increased analytical variability but **comparability ensures no clinically meaningful differences** (ICH Q5E)




Vezer et al., Curr Med res Opin. 2016; 32(5):829-34 / Uhlig and Goll., Rheumatology. (56) 2017

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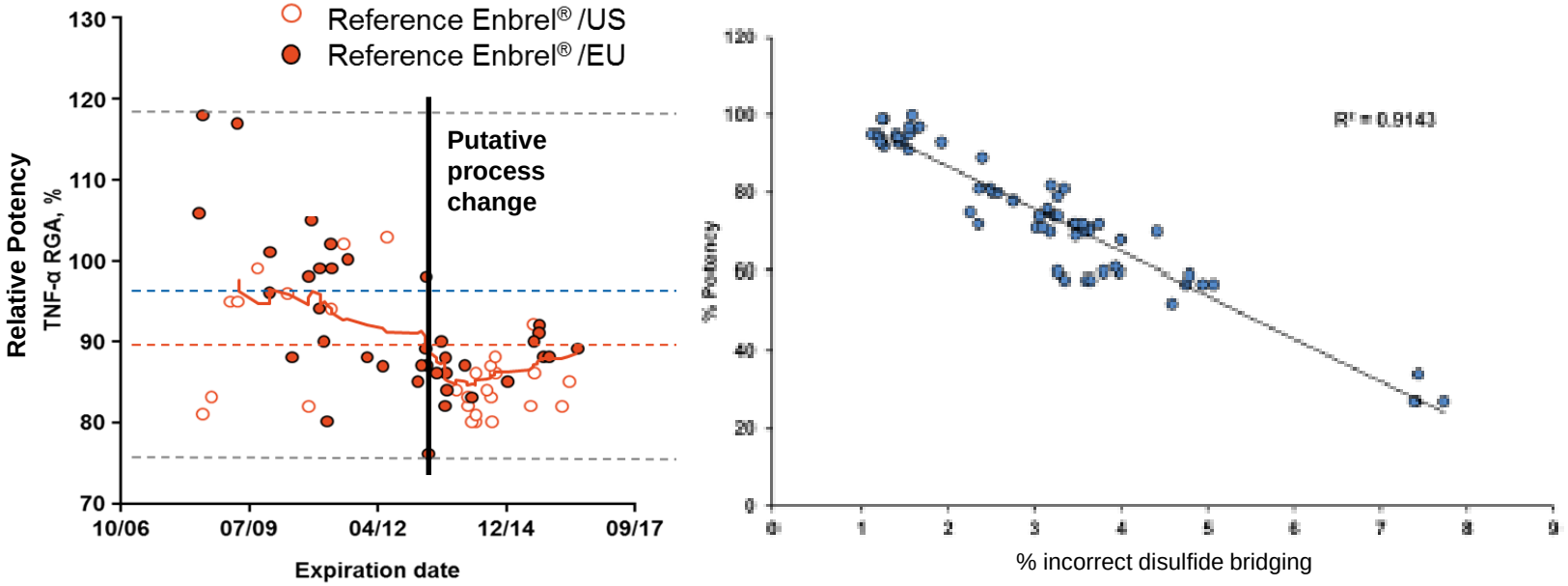
# Etanercept reference medicine structure–function shifts

- *In vitro* potency shift correlates with changes in % incorrect disulfide bridging (putative process change)
- Not clinically relevant because *in vivo* potency not impacted




RGA, reporter gene assay; TNF, tumor necrosis factor

The red line indicates the moving mean as calculated by 11 to 21 data points

Lamanna et al., Scientific Reports (2017) 7: 3951



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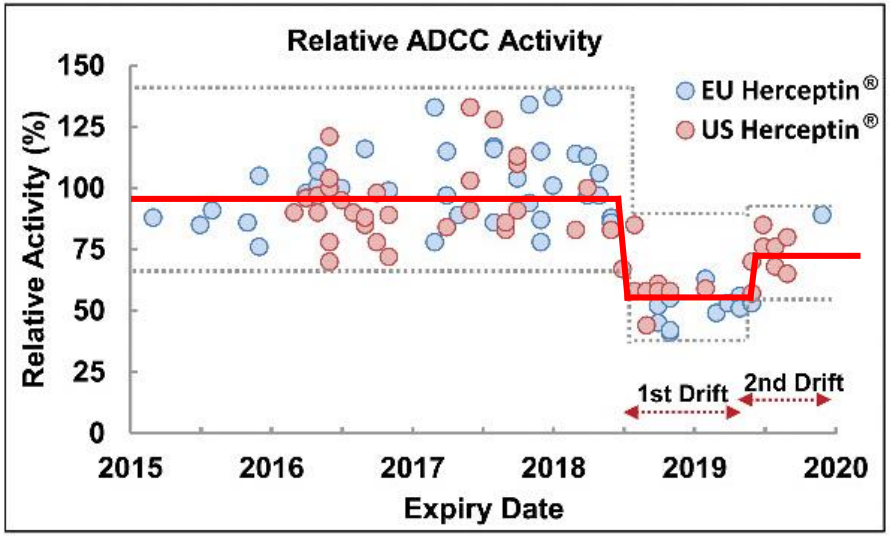
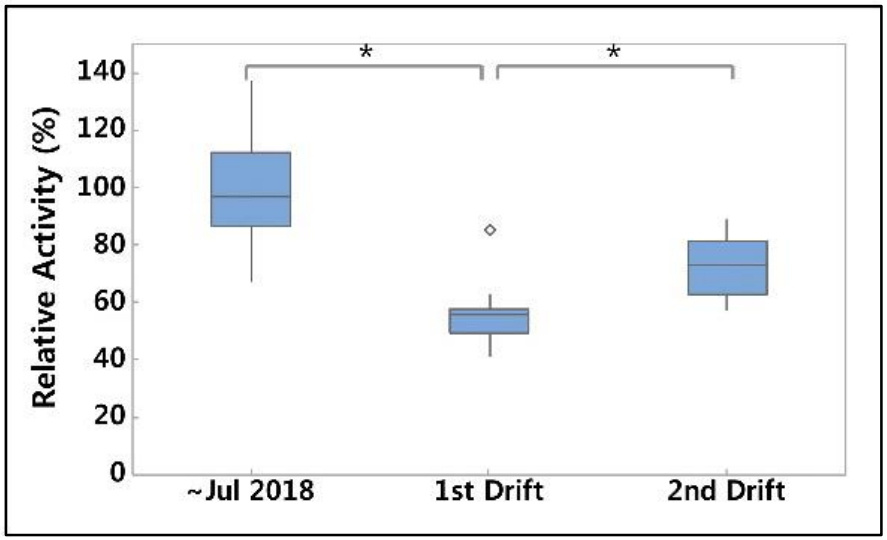
# Trastuzumab reference medicine structure–function shifts

- Shift in mean values (putative process changes)
- Shift in sensitive analytical data does not automatically imply a clinical shift
- Comparability ensures no clinically meaningful difference




ADCC, antibody-dependent cell-mediated cytotoxicity
Kim et al. *Mabs,* 2017; 9. 704-714.

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# Implications ….

- Different lots of the same biologic are on the market at the same time that vary in quality attributes
  - Patients are switched without concern

- No change in product label – indicating comparable safety and efficacy extrapolated to all indications





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# How common are process changes with a clinical impact?

- From 1982 - 2017:
  - 261 recombinant protein therapeutics in the US and Europe were identified that underwent a process change
  - Only three cases of clinical drift were suggested
    - Erbitux® (cetuximab)
    - Eprex® (erythorpoeitin)
    - Rebif® (interferon beta-1a)
  - Only a single verifiable case of product variability (Eprex®) that led to adverse events

~1% of products, but since most products had multiple process changes, the incidence of process changes with clinical relevance is extremely rare.

Lamanna et al. Exp Op Biol Ther (2018) 18:369-379

Erbitux® is a registered trademark of ImClone LLC
Eprex® is registered trademark of Centocor Ortho Biotech Inc.
Rebif® is a registered trademark of EMD Serono, Inc.

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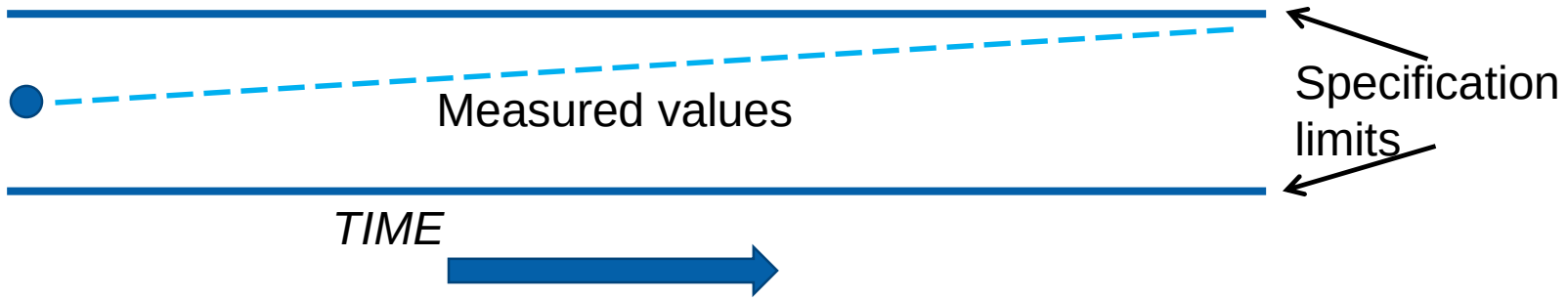
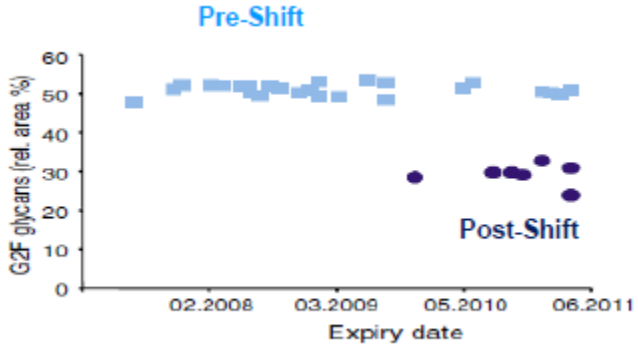
# Process variability
# Drift *vs.* Shift

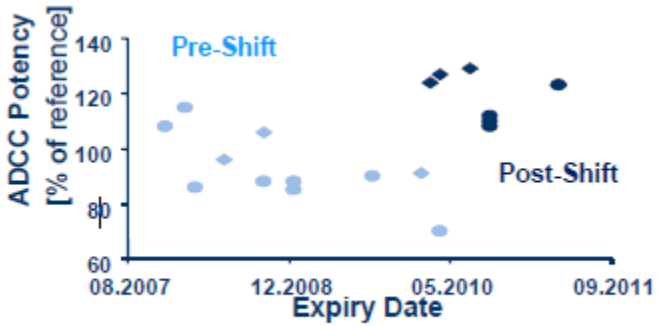
**Drift** = gradual, directional change in a quality attribute over time

- Drift beyond acceptable limits is prevented by control strategies & quality systems




**Shift** = Abrupt changes in a quality attribute as a result of a manufacturing change




*Schiestl M, et al .Nature and Biotechnology, 2011, 29 (4): 310-12*



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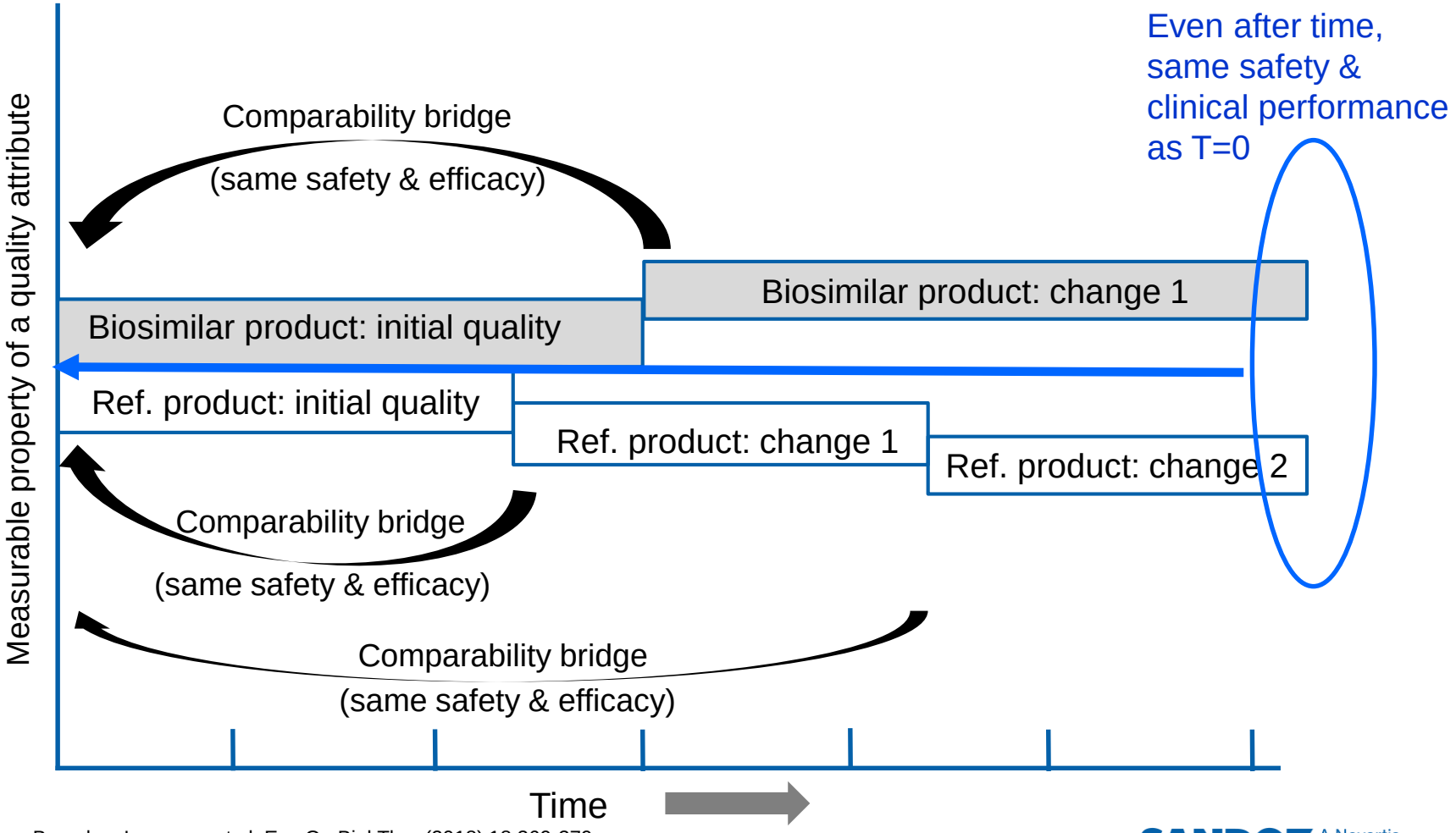
# Shifts are inherent to biologics: Comparability ensures the maintenance of clinical safety and performance




Based on Lamanna et al. Exp Op Biol Ther (2018) 18:369-379

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# Divergence due to Drift or Shift

Could drift and shift contribute to changes in the clinical attributes and consequently, over time, to clinically meaningful differences

- between an originator and a biosimilar?
- between a product and it‘s label claim?

- Biosimilarity and interchangeability are established once, and is always relative to the reference product as evaluated at time of approval
  - Changes in quality attributes always need to justified by the sponsor, who must prove to health authorities that the changes have no impact on safety or efficacy. Applies equally to originator and biosimilar





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# Agenda

- What and why of variability
  - Normal variability, deviations, drift & shift
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  - Reference standards
  - Comparability
  - QbD & Process Design
  - Continued Process Verification

GMP, good manufacturing practices; QbD, quality by design





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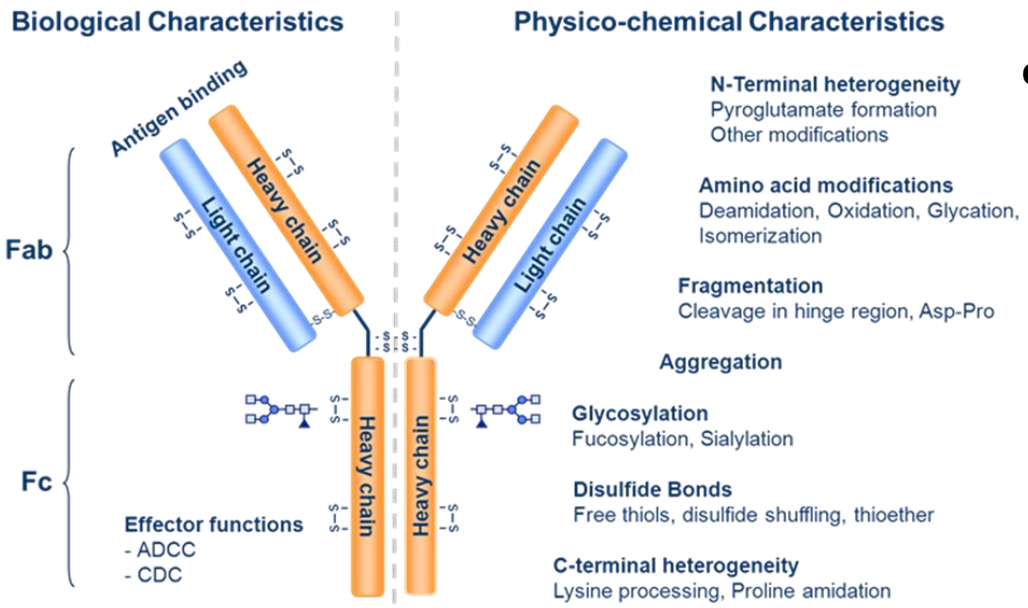
# Stringent control of clinically meaningful quality attributes through Quality by Design




**Assessment on clinical relevance**

- **Immunogenicity**
- **Safety/Toxicity**
- **Pharmacokinetics**
- **Potency**

**Criticality reflects clinical relevance and dictates the degree of product and process control**

**Criticality**

- **Very high**
- **High**
- **Moderate**
- **Low**
- **Very low**

**Existing knowledge**

- **Literature**
- **In-house studies**
- **Related molecules**

Sandoz internal QbD strategy in accordance with ICH Q8 (Pharmaceutical Development)

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# Pharmaceutical Quality System & cGMP

## Multi-system inspection model


*

## Pharmaceutical Quality System

according to FDA guidance and ICH Q10

**Objectives:**

- Achieve product realization
- Establish and maintain a state of control
- Facilitate continual improvement

**Elements:**

- Process performance and product quality monitoring system;
- *Corrective and preventive action* (CAPA) system;
- Change management system;
- Management review of process performance and product quality

- No difference in cGMPs or quality system for biosimilars vs originators
- Delivering product of consistent & defined quality is at the core of GMP & PQS

FDA Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations
ICH Q10 Pharmaceutical Quality System
cGMP, current good manufacturing processes; PQS, pharmaceutical quality systems

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# Setting specifications

- "Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval." *
- "It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use" *
- Specifications are linked to the manufacturing process
- Specifications are linked to preclinical and clinical studies
  „The quality of the material made at commercial scale should be representative of the lots used in preclinical and clinical studies."

Specifications establish a link to the lots tested in clinical studies and links commercial quality to the label claim

* ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073488.pdf (accessed 24 Aug 2018)

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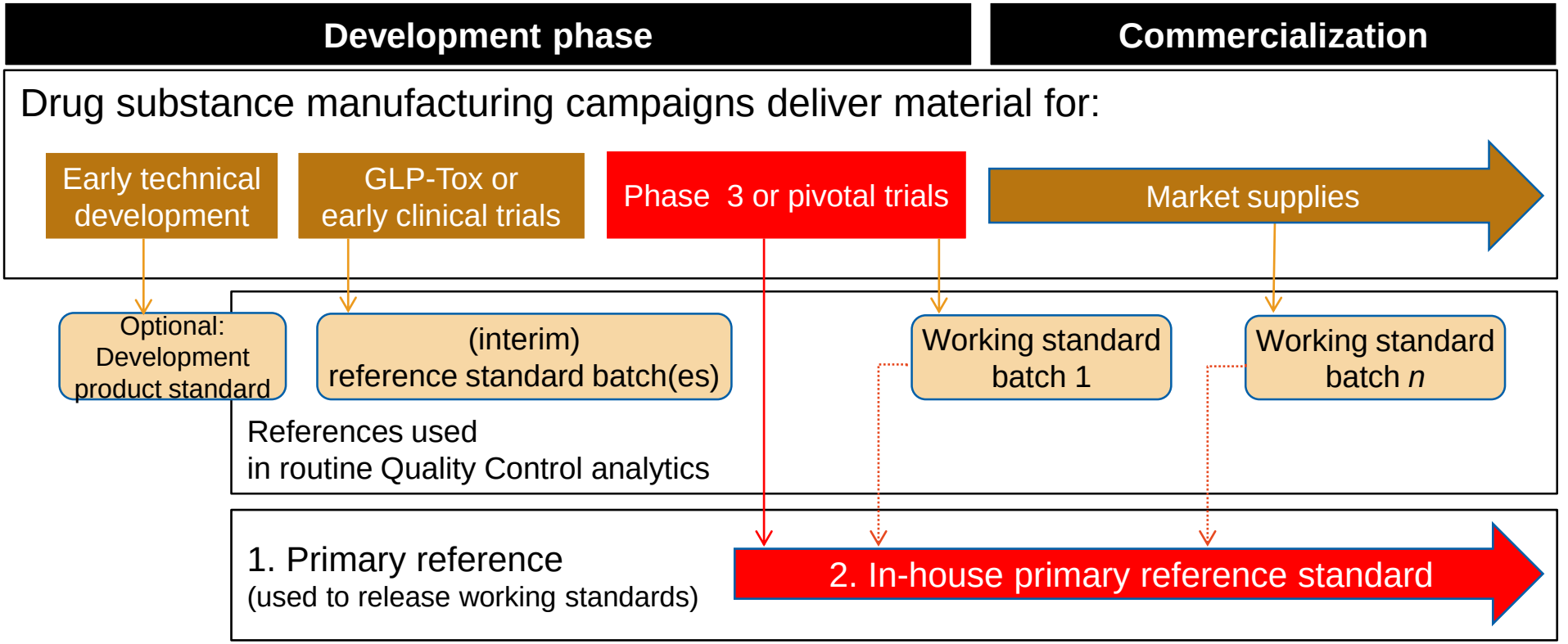
# Reference Materials / Standards
## *- keeping the clinical lots as reference point*

Two different tiers of reference standards (as per ICH Q6B)




Two-tiered in-house reference standard keeps the link of the working standards to the lots tested in clinical studies

adapted from M. Blümel, CMC Strategy Forum Summer 2013; Option A

# Comparability exercises to assess manufacturing changes

**ICHQ5E: Comparability of biotechnological/biological products subject to changes in their manufacturing process**

"The goal of the comparability exercise is to ensure *quality*, *safety* and *efficacy* of drug product produced by a changed manufacturing process…"

"A determination of comparability can be based on a combination of *analytical testing*, and, in some cases, *nonclinical* and *clinical data*."

"The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar…"

ICH Q5E https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed 24Aug2018)

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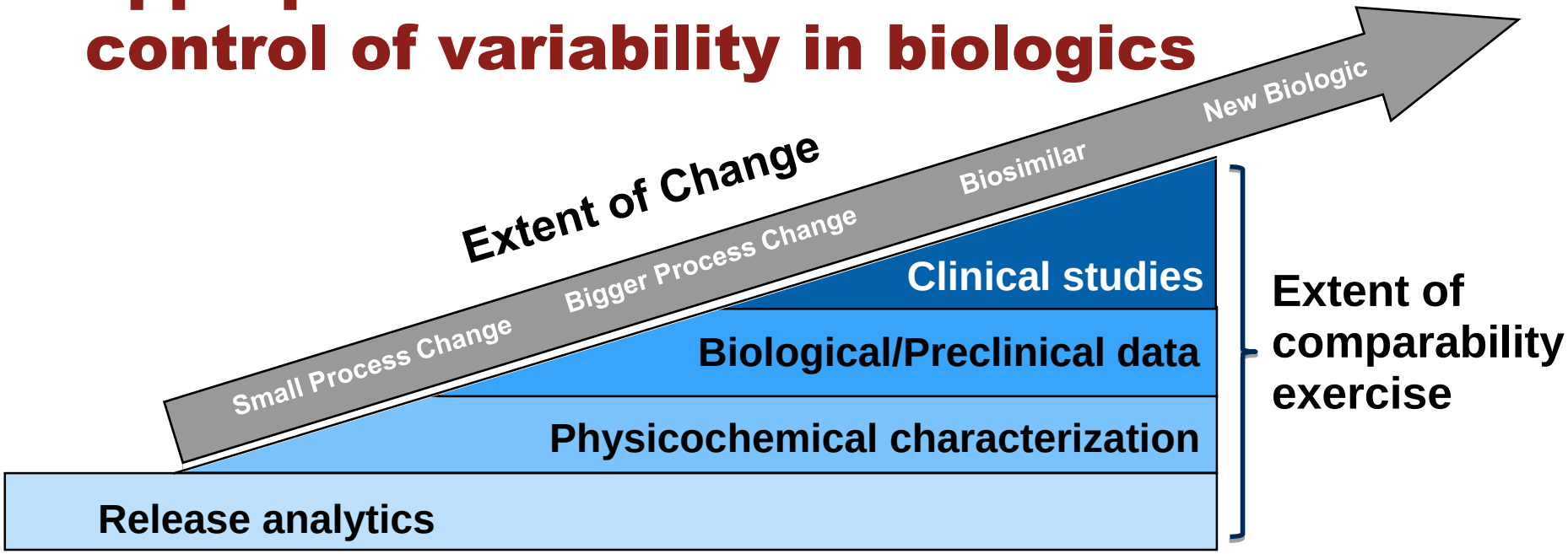
# Continuum of comparability allows for appropriate control of variability in biologics




- Comparable ≠ Identical
- However, an originator biologic after an approved manufacturing change is as safe and efficacious as the pre-change product [1]
- However, an approved biosimilar has no clinically meaningful differences compared to the reference product [2]

1 ICH Q5E https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed 24Aug2018)
2 Scientific Considerations in Demonstrating Biosimilarity to a Reference Product https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf (accessed 24 Aug 2018)

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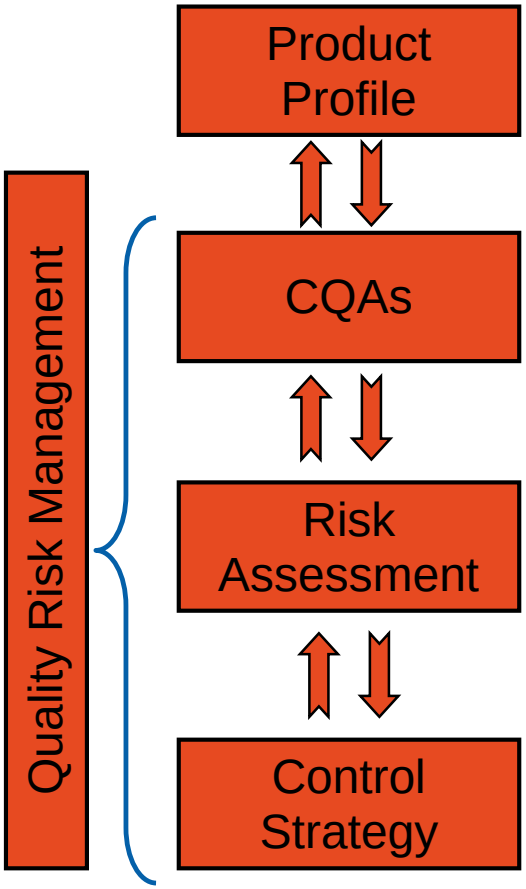
# Quality by Design (QbD) – bringing Product and Process Understanding together




Define the Quality Target Product Profile

Determine the Critical Quality Attributes (**CQA**)

Link material attributes and process parameters to CQAs and define Critical Materials, Critical Material Attributes and Critical Process Parameters

Design and implement a **Control Strategy** based on process & product understanding

ICH Q11 Development and Manufacture of Drug Substances

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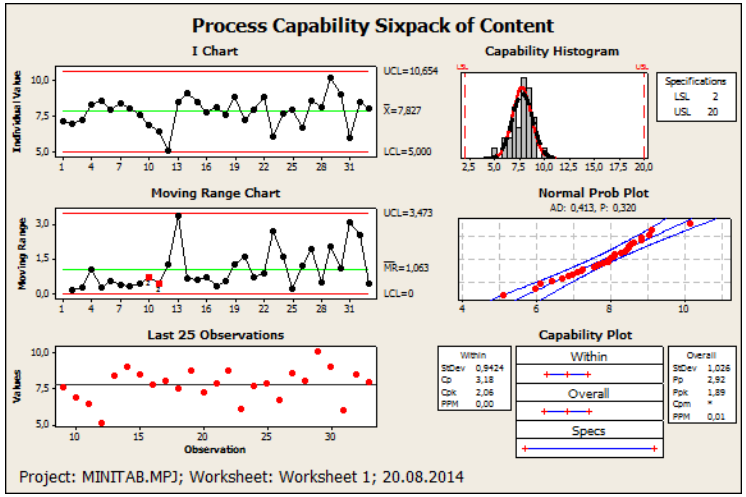
# Continued process verification

An alternative approach to process validation in which manufacturing performance is continuously monitored and evaluated.

- Continual assurance that the process remains in a state of control (the validated state)
- An ongoing program to collect and analyze product and process data that relate to product quality



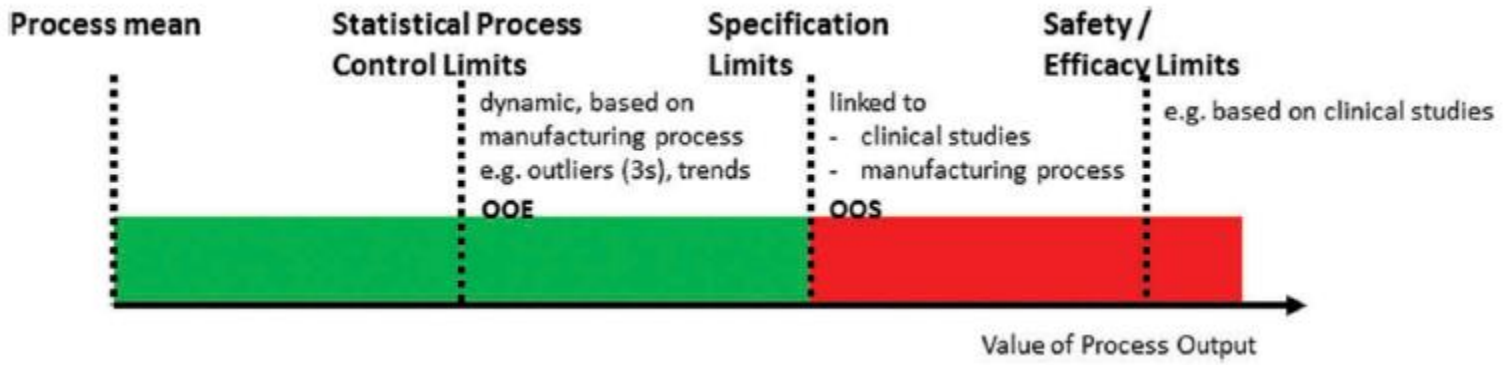

Statistical analysis for

- distribution
- outliers
- trends
- patterns
- process capability

Allows for proactive quality assurance rather than reactive quality control

ICH Q8R2 Pharmaceutical Development

# Strategic overview of continued process verification




- Allows fast & objective identification of outliers and trends
- Statistical process control limits (commonly 3 SDs above mean) define out-of-expectation
- Allows for corrective action to be taken before outliers reach specification limits

OOE, out-of-expectations; OOS, out-of-specifications

Lamanna et al. Exp Op Biol Ther (2018) 18:369-379

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# Conclusions – control of manufacturing variability

- A quality system prevents divergence between a biologic and its label claim
- A quality system prevents divergence between pre- and post-change biologics, biosimilars and reference products, and interchangeably used biologics
- Successful tools & concepts for controlling pharmaceuticals combined with considerable improvements over the last decade
  - QbD, Quality System, Risk Management
  - Analytical technology
  - Comparability, reference standards, specifications, process validation incl. continued process verification





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# Summary

- Biosimilars must demonstrate high analytical similarity and must exhibit equivalent safety and clinical performance
  - Totality of evidence from analytical & clinical comparisons used to demonstrate biosimilarity
- Biosimilars are developed in a step-wise manner to fall within the variability of the originator
  - Variability is inherent to originator and biosimilar biologics, however safety and clinical performance must remain consistent throughout the product lifecycle
- Originator and biosimilar biologics employ quality systems and must comply with regulatory frameworks to maintain consistent clinical performance
  - Strong structure – function understanding combinded with robust quality systems such as Quality by Design ensure consistent quality
  - The comparability requirement following manufacturing changes ensures equivalent clinical performance throughout the product lifecycle
- Over a decade of market experience in the EU underscores the safety and utility of the biosimilar concept
  - 50 approved biosimilar products to 15 different originators in the EU

European Comission Consensus Information Document. What you need to know about Biosimilar Medicinal Products. http://ec.europa.eu/DocsRoom/documents/8242/attachments/1/translations/en/renditions/native
Lamanna et al., Maintaining consistent quality and clinical performance of biopharmaceuticals. Expert Opin Biol Ther. 2018
http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe (accessed 24Aug2018)

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# To revisit the question …

## Can variability in quality attributes over time cause clinical differences?

Answer: Lot to lot variability is controlled by implementation of a strong process quality system

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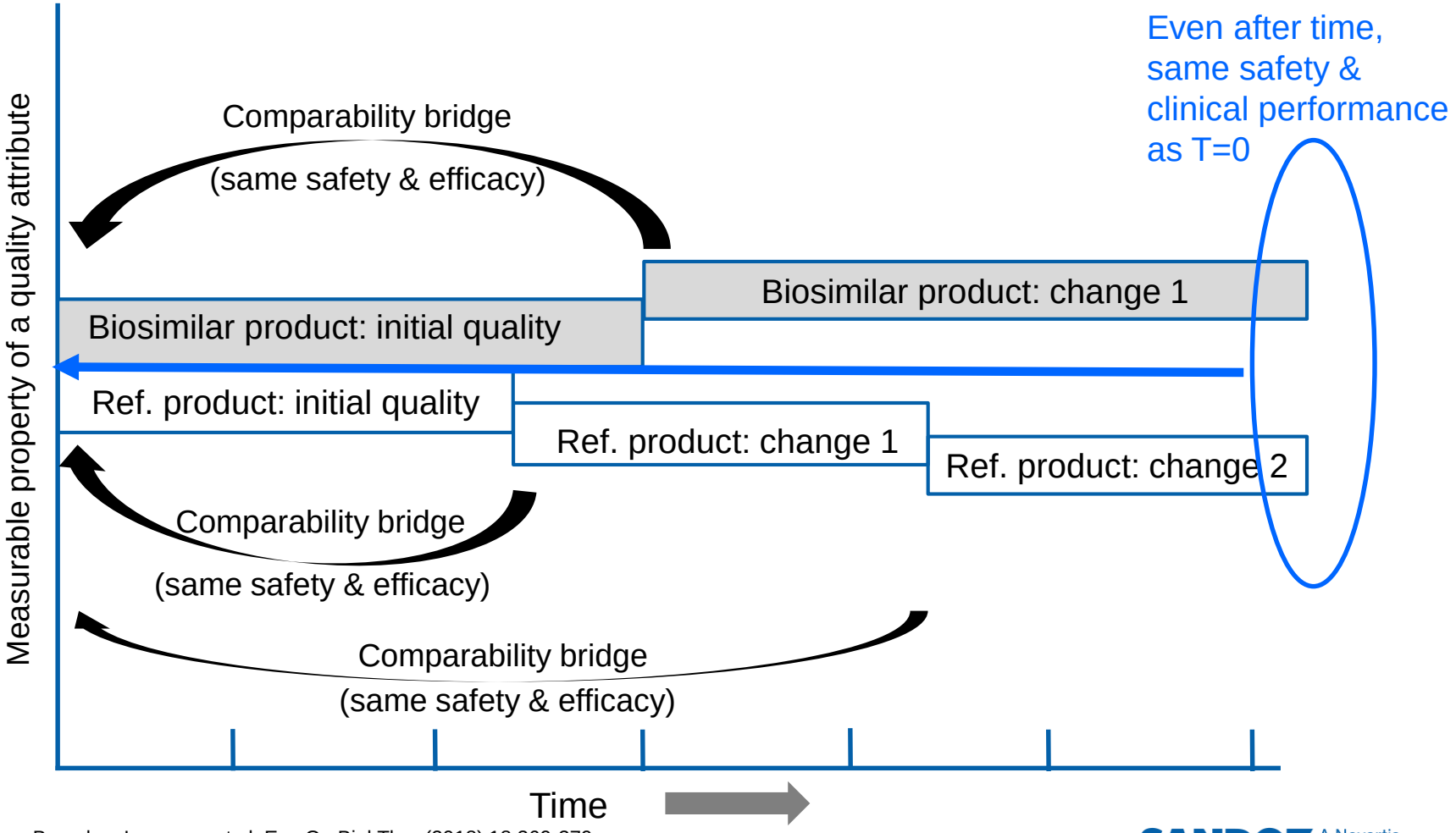
# Variability due to process changes:

Comparability bridging ensures maintenance of clinical safety & performance




Based on Lamanna et al. Exp Op Biol Ther (2018) 18:369-379

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# Take home messages

Post-approval, manufacturing variations and variability of biosimilars and interchangeable biologics should be regulated as any other biological drug

1. Should not need to re-establish biosimilarity or interchangeability after a set period of time
2. Should not need to automatically require clinical bridging studies as a condition of approval of manufacturing changes.

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# Thank you

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