A regulatory perspective on stability studies supporting comparability of therapeutic protein products

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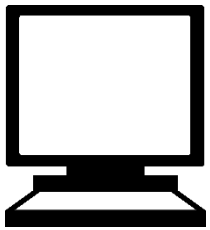
Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



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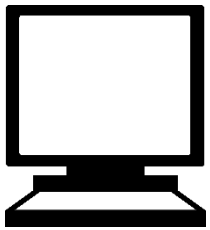



Drugs are no different.


FDA
Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence in their *next* dose of medicine.

Presentation Outline

- General concepts for comparability and stability.
- Our view on stability assessment to support comparability based on case studies from different stages of product development lifecycle.

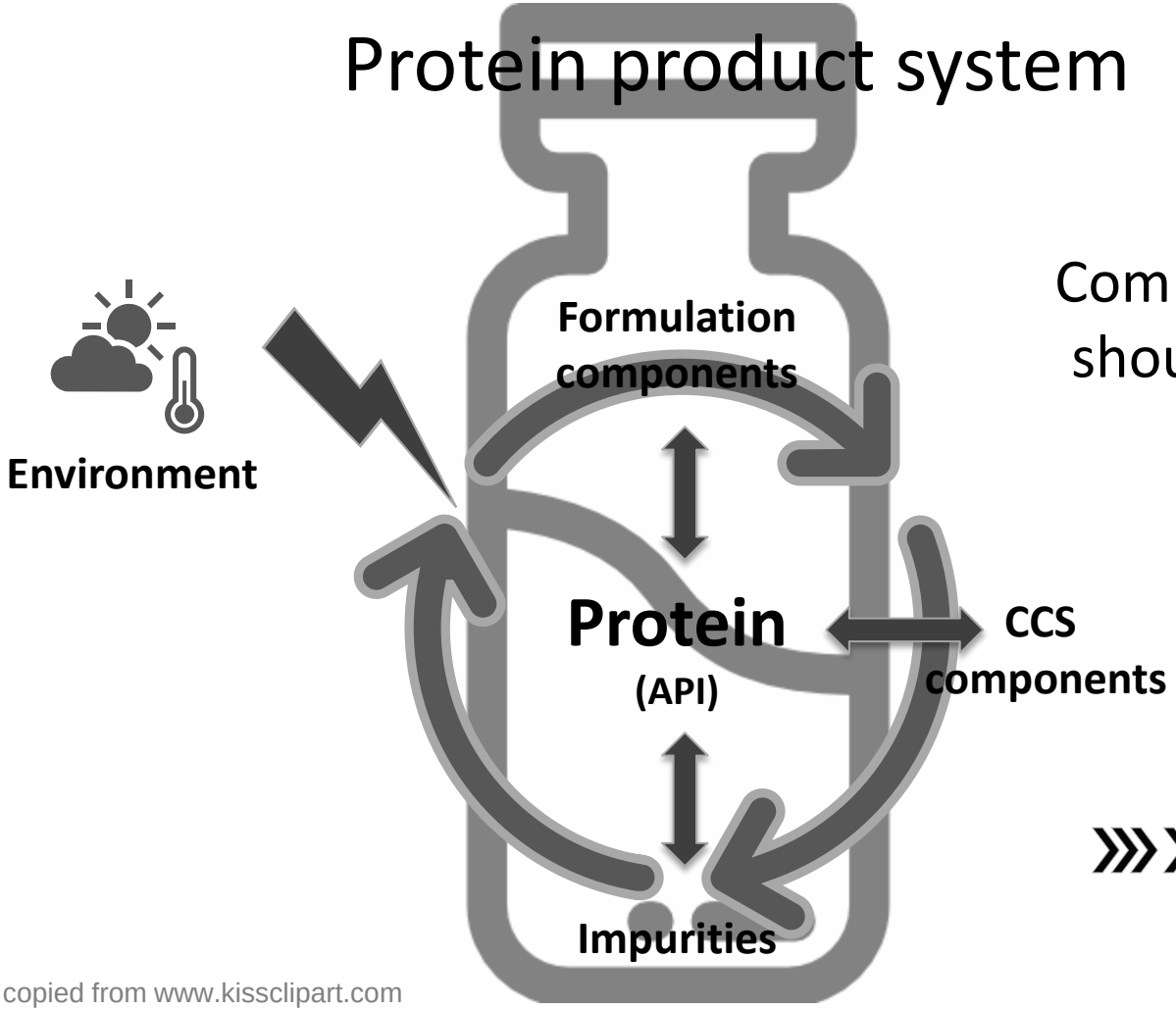
This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Common manufacturing changes throughout development

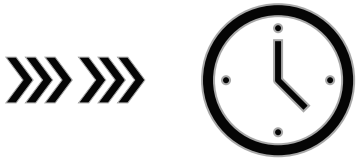
- Manufacturing scale up
- New manufacturing site
- Process improvements (and new technologies)
- New cell bank
- Formulation and presentation changes
- Changes to raw materials, equipment

Risk assessment used to assess the potential impact of changes on product quality as it relates to safety and efficacy.

Protein product system



Comparability assessment should consider all these interactions and components.



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Comparability: General principle

ICH guidance document Q5E

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* and that the existing knowledge is sufficiently predictive to ensure that **any differences in quality attributes have no adverse impact on safety or efficacy** of the drug product.

* As defined in ICH Q5E

Comparability: Studies

Analytical
- Structure
- Function
- Impurity Profile
- Molecular Heterogeneity
- Stability

Non-clinical
- Toxicity
- PK/PD
- Tissue Cross Reactivity

Clinical
- PK/PD
- Safety and Efficacy
- Immunogenicity

ICH Q5E:

- If a manufacturer can provide assurance of comparability through analytical studies alone, non-clinical or clinical studies with the post-change product are not warranted.
- However, where the relationship between specific quality attributes and safety and efficacy has not been established, and differences between quality attributes of the pre- and post-change product are observed, it might be appropriate to include a combination of quality, non-clinical, and/or clinical studies in the comparability exercise.

Analytical comparability assessment

Product comparability may include:

- Release testing
- Extended characterization*
- Stability studies (real-time, accelerated/stress*)

*May be limited during early development

ICH Q5E “Stability studies might be able to detect subtle differences that are not readily detectable by the characterization studies.”

Stability studies for comparability

The need, extent and type of stability studies depend on:

- product development stage,
- product and process knowledge,
- extent of change,
- potential impact of the change on product CQAs, and on safety and efficacy,
- availability and capability of analytical methods.

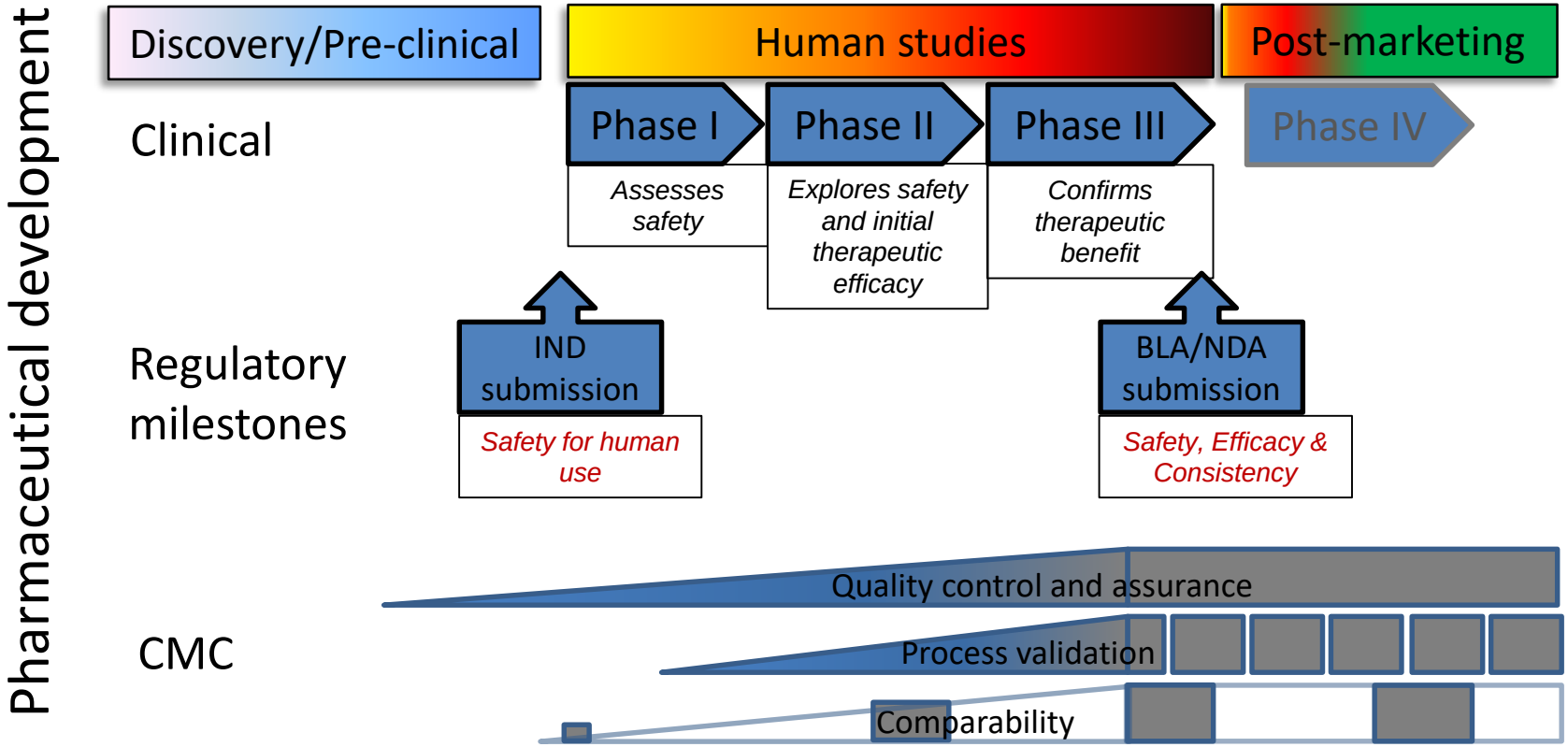
Stability studies for comparability

- At accelerated or stress conditions:
  - To discover potential differences in the degradation rates and/or pathways of the pre- and post-change products,
  - Should be designed to provide meaningful information (ICH Q5C and Q1A(R)):
    - Tested for shorter time course, but sufficient to capture changes
    - Include sufficient timepoints (to overcome assay variability)
    - Include conditions that result in incremental changes over the study time
    - Include all potential stability-indicating assays.
- At recommended storage condition:
  - For comparison of stability profile of the pre- and post-change product,
  - To confirm shelf life of an approved product at post-change
    - Limited data may be available at the time of submission.

Stability comparability studies at different stages of product lifecycle
&
Case studies

Product lifecycle

** Typical original product*



Typical stability studies for comparability for initiation of or during phase 1 IND

- At this stage, limited product and process knowledge (including non-clinical data), no clinical experience, analytical methods are not validated or stability-indicating methods are not defined, limited number of lots.
- Minimal comparability stability data may be needed depending on extent of change and potential impact of change on safety, e.g.:
  - For initiation of FIH study, no comparability stability data is required,
  - If some clinical safety data are obtained using pre-change material, comparability of 1 lot each of pre- and post-change material at accelerated/stress condition may be needed.

  Enroll post-change lot into real-time stability program.

Case study 1: Original IND for FIH study

- An original IND for mAb product
  - 1 toxicology lot and 1 clinical lot manufactured by processes with minor differences, in different scales
- Comparability (toxicology vs clinical material):
  - Release data and limited characterization, no specific stability assessment
  - No significant difference that would affect safety
- Stability data: limited results at real-time, accelerated and stress conditions
- IND is safe to proceed from CMC perspective.

Note: Comparability assessment for initiation of an IND should support that clinical material(s) is comparable to the material(s) used in toxicology studies (i.e., relevancy of the toxicology data) and does not contain additional toxicity potential (e.g., process and product impurities, variants).

Typical stability studies for comparability during phase 2

- At this stage, there is progress in all drug development aspects: increased product and process knowledge, accumulated non-clinical and clinical data. Analytical methods may not be validated, but data have identified stability-indicating methods. Still limited number of lots are produced.
- Depending on extent of change, potential impact of change on safety and dosing the following stability data are needed for comparability:
  - Comparison of at least 1 lot each of pre- and post-change product
  - Data from accelerated/stress study (in side-by-side setting)
  - Enroll post-change lot(s) into real-time stability program.

Case study 2: IND at the end of phase 2

- An IND amendment for mAb product
- Changes in cell bank (limited-dilution cloning) and DS manufacturing (scale-up)
- Comparability pre-change lots vs post-change lot:
  - Release and limited characterization data
  - Real-time stability data for a limited time, no accelerated/stress study
  - No significant difference
- Stability program: limited real-time, accelerated and stress data (i.e., performed at different times, conditions, not in side-by-side).

- *Assessment:* The provided data are insufficient to demonstrate comparability at this stage of development:
  - Requested to provide comparability data of the pre- and post-change DS lots from accelerated/stress study performed in side-by-side setting
  - Enroll post-change DP lot(s) into real-time stability program.

Note: Need of appropriate comparability stability data to support that the post-change product is comparable to pre-change materials.

Typical stability studies for comparability during or after phase 3 and post-marketing

- At this stage, substantial product and process knowledge is available, including non-clinical, and safety and efficacy data. Analytical methods are validated, stability-indicating assays are identified, a number of “pre-change” lots should be available.

- Depending on extent of change, its potential impact on safety and efficacy the following should be included in the comparability package:
  - Comparison of at least 3 lots each of pre- and post-change product
  - Data from accelerated/stress stability studies (in side-by-side setting, or compared against comparability acceptance criteria defined by historical data).

  Enroll post-change lot(s) into real-time stability program and have some data compared to historical data to support approval and expiration dating.

Case study 3: Post-marketing

- A supplement for DS process change (mAb product)
- Comparability data:
  - 4 post-change lots vs multiple pre-change lots
  - Comparability acceptance criteria based on historical data
  - Stability data: 9 months at -70°C and 5°C, and 1 month at 25°C
- Degradation trends for charge variants at stress (25°C) condition were different between the post- and pre-change lots, as well compared to data in the original BLA
  - Explanation received: temperature control of the stability chamber was inaccurate.
- Supplement was not approved due to uncertainty of comparability.
- Data from a new stress study was required to show comparability.

Note: Importance of control over study details (in this case, equipment temperature) and results (new vs previous trends).

Case study 4: Post-marketing

- A supplement for approved mAb product
- Changes: re-cloning of MCB, modified DS process, new DP facility
- Analytical comparability data (under CPs):
  - Pre- vs post-change lots: 3 vs 3 DS lots, multiple DP lots
  - DS and DP stability data: up to 12 months in all stability conditions
  - Minor difference in DS fragmentation (and charge profile at release)
  - Faster DP degradation (intact IgG) at recommended and accelerated conditions.
- Clinical comparability study: PK and safety → no difference
- Supplement is approved with shortened DP shelf life and with DS/DP combined expiry (DP lots are manufactured from 3-month old DS lots).

Note: Considerations for planning of changes, real-time stability data may be needed to define the shelf life after change.

Case study 5: Post-marketing

- A supplement for product with potential drug shortage
- Changes: New DP fill site with facility fit (process hold vessel) and container closure (type 1 vial molded → tubular)
- Comparability data:
  - 4 post-change lots vs multiple pre-change lots
  - Stability data: 3 months at recommended and accelerated conditions
  - No noticeable difference at either condition
- Supplement is approved.

- Aggregate results are OOS by 18-month in post-change PV lots
- Outcome: Shortened the DP shelf life.

Note: Accelerated stability data are not always predictive of real-time stability.

Summary

- Stability assessment for comparability has specific purpose (differs from typical studies in the stability program):
  - To determine potential differences in the degradation rates and/or pathways and to compare the stability profiles of the pre- and post-change product,
  - To confirm shelf life of approved product at post-change.
- Major differences between the scope and design of comparability stability studies for drugs in early and later stages of development.
- Careful planning for manufacturing changes:
  - Encourage implementation of major changes prior the pivotal clinical studies,
  - Preserve pre-change material and a well-characterized RS under appropriate conditions to maintain quality.

Acknowledgments

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