Building a Comparability Strategy for a Major Post-Approval Manufacturing Change

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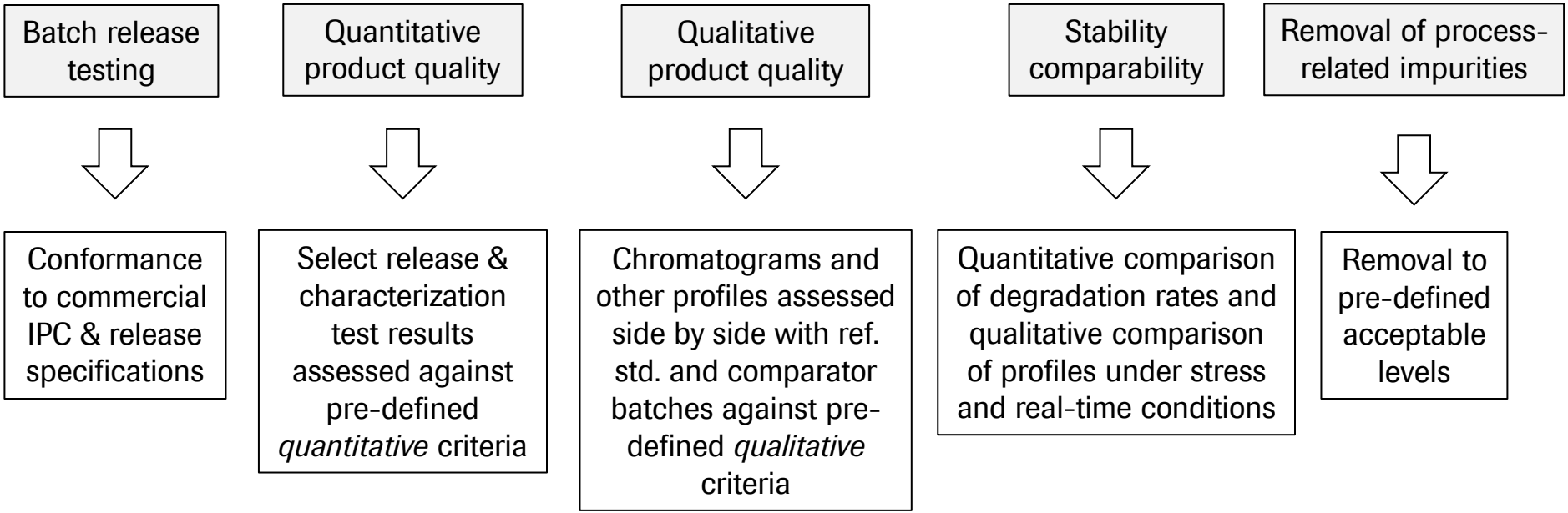
Motivation & Outline

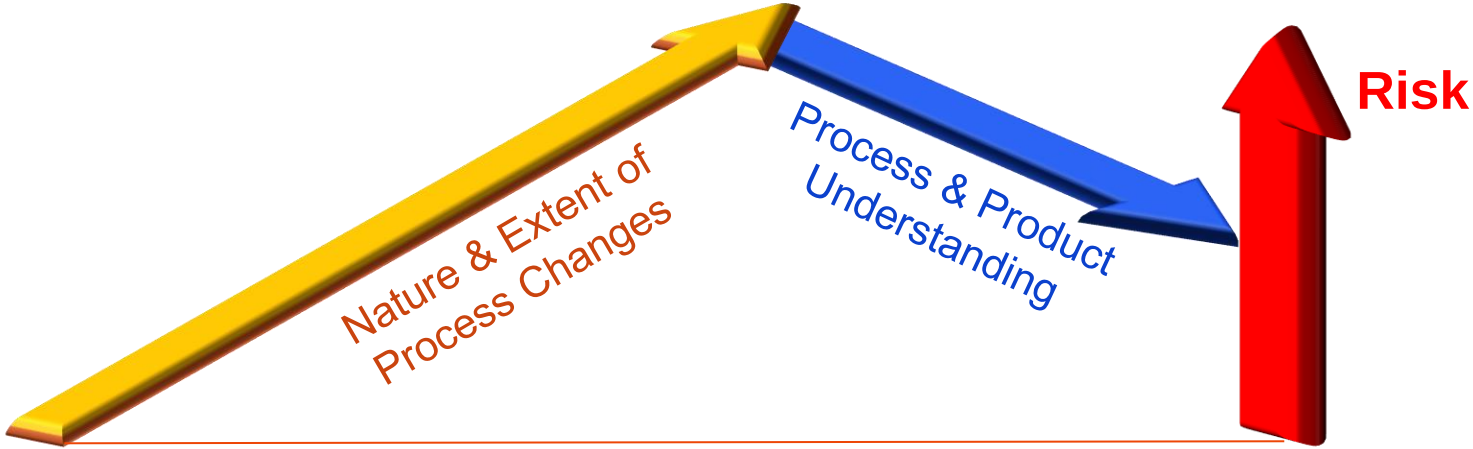
Process changes happen of necessity, major process changes are a choice and opportunity. All of them need to demonstrate comparability.

- Addressing CQAs at risk due to the change
- Addressing comparability during validation, and development
- Assess at the point of change, and effect on patients
- Think… test, test, test… think

Standard Analytical Comparability Elements



Major Process Changes, Big Comparability Exercises



Enhancements mitigating risk for major changes

- Additional quality attributes assessed
- More extensive “extended characterization” methods
- More sophisticated basis for quantitative comparability criteria

Dealing with CQAs at risk due to the change

Which CQAs may be affected depends on nature and extent of the change but…

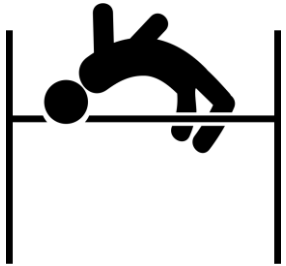
- CQAs are NOT created equal, and do not exist in isolation
- Comparability assessment is on the totality of data.

Category	Intent	Examples
A	Attributes that can't be justified as no adverse impact if outside pre-change product range	Analytical results that are measures of bioactivity and/or most impact MOA
B	Attributes that might be justified as acceptable if outside pre-change product range	Analytical results that are measures of, or represent CQAs, but actual ranges are not near a clinically relevant limit.
C	Attributes that are non-CQAs or not amenable to statistical analysis	Analytical results for non-CQAs or that are pass/fail or qualitative

When does the comparability exercise start?

During development:
The targets to aim for

During validation:
The bar that must be met



Cat.	During development	Comparability Protocol & Report
A	Results outside pre-change product range: Thou shalt continue development	Individual values outside range potentially justifiable, average value outside range is likely “not comparable”
B, C	Results outside pre-change product range or not consistent: Consult cross-functional SMEs if observed values justifiable, considering totality of attribute results.	Results outside range or not consistent with pre-change product must be justified as acceptable based on product knowledge and/or further evaluation, and considering totality of results.

Leverage the growing body of product & process knowledge

Manufacturing Experience, Process Knowledge

Clinical Experience, Product Knowledge

1st Indication

2nd Indication

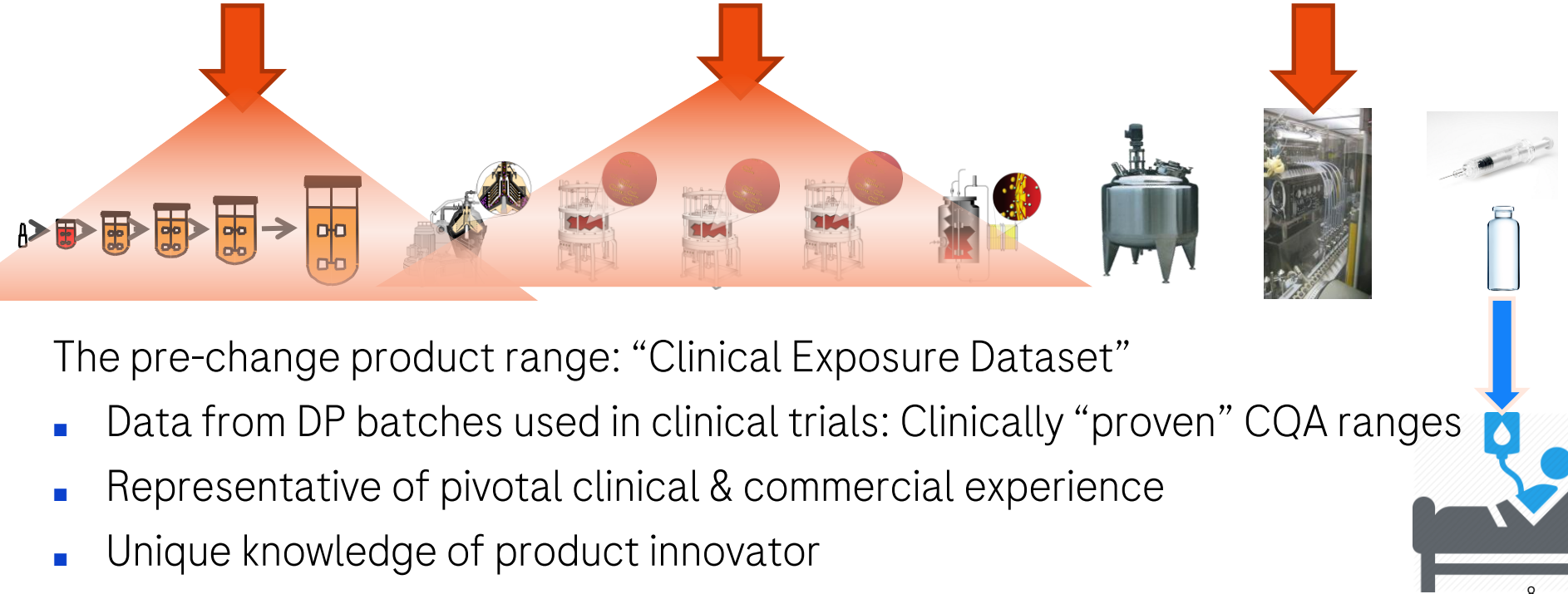
1st Line Metastatic

Adjuvant

Neoadjuvant

Comparability at the point of change… and relevant to the patient

Analytical assessment of the evaluable pool closest to the change



The pre-change product range: “Clinical Exposure Dataset”

- Data from DP batches used in clinical trials: Clinically “proven” CQA ranges
- Representative of pivotal clinical & commercial experience
- Unique knowledge of product innovator

Analytical Results and Analysis

Quantitative

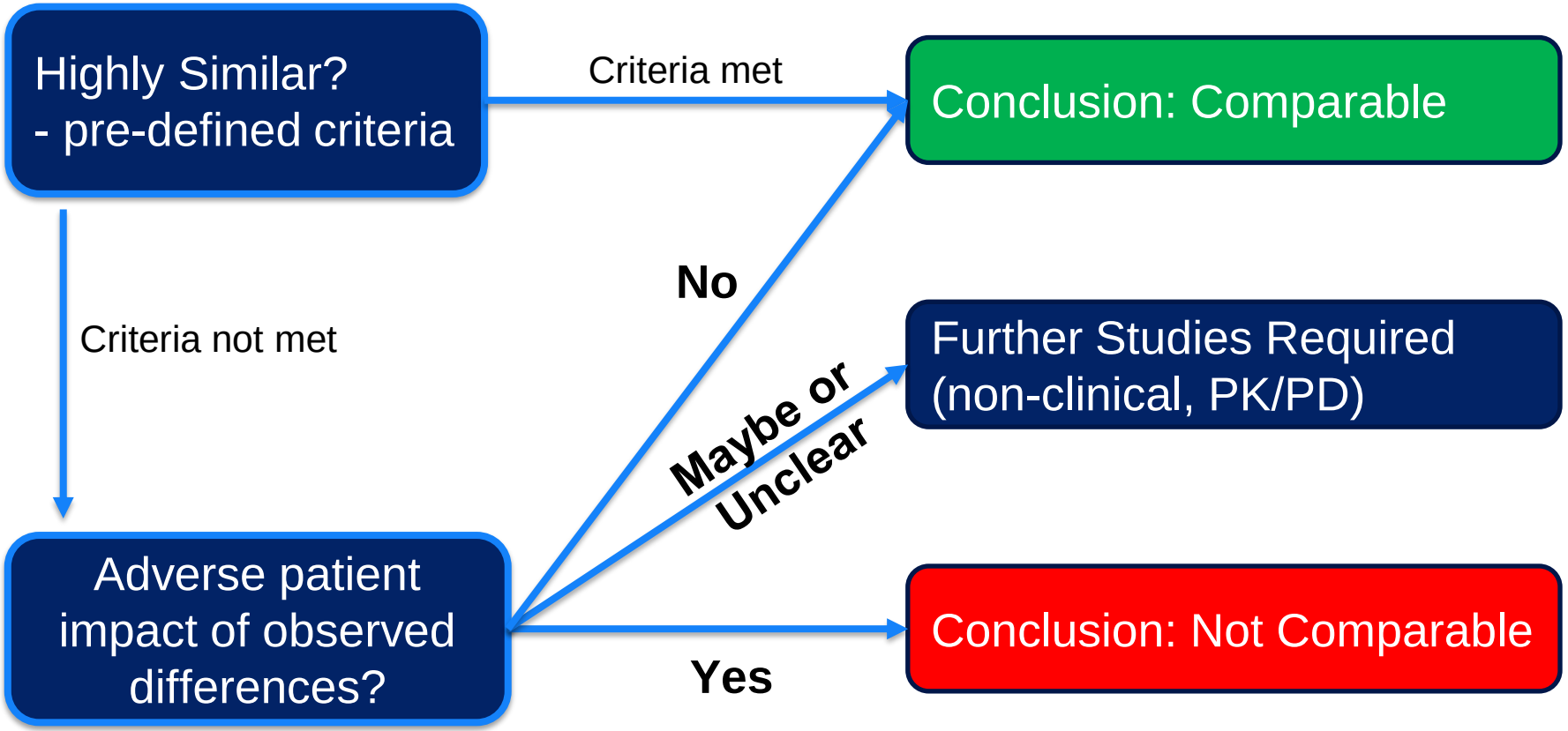
- Ranges based on Clinical Exposure Dataset
- Trend Chart evaluation of post-change vs. pre-change batches

Qualitative

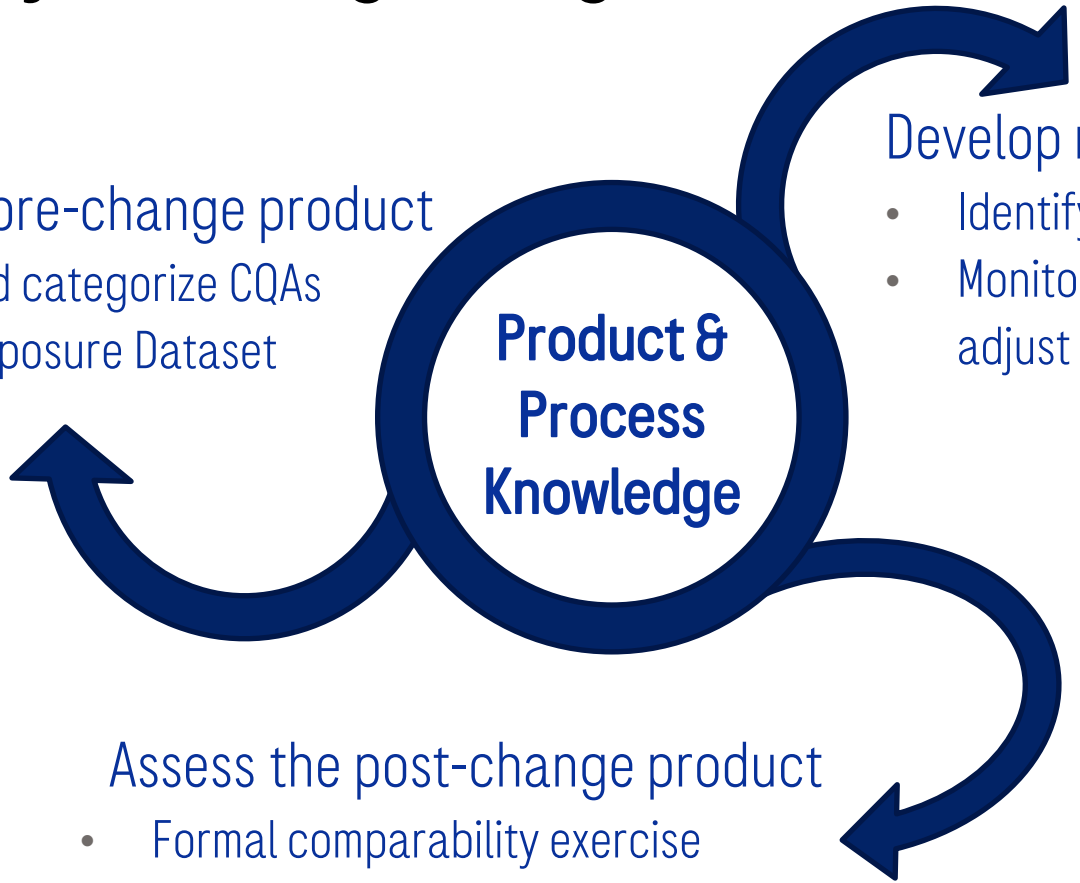
- No new peaks, similar peak shapes & retention times, same rank order
- Chemometric analysis (potentially)
- Comparison to reference standard & pre-change comparator batches

Criteria describe “high similarity” to the pre-change product, not necessarily the limit of failure

Outcomes


Highly Similar?
- pre-defined criteria
Criteria met
Conclusion: Comparable
Criteria not met
No
Maybe or
Unclear
Further Studies Required
(non-clinical, PK/PD)
Adverse patient
impact of observed
differences?
Yes
Conclusion: Not Comparable

Summary & Closing Thoughts



Define the pre-change product

- Define and categorize CQAs
- Clinical Exposure Dataset

Develop major process change

- Identify impacted CQAs
- Monitor comparability results, adjust process as needed

Assess the post-change product

- Formal comparability exercise
- CQA relation to clinical performance