Risk-based Comparability for Biological Products
(Perspectives from a multi-national company)

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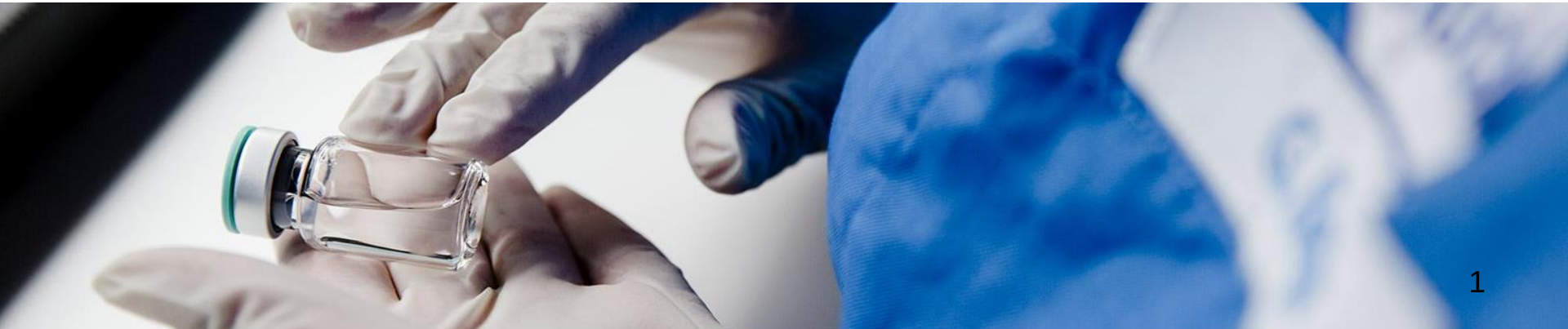


Outline

- The importance of comparability to a multinational company's ability to supply drug throughout the product lifecycle.
- Example of how comparability concepts enabled a product's 20+ year journey as a marketed product.
- Leveraging risk-based comparability concepts highlighting a drug substance site transfer example.
- Key takeaways.

THE JOURNEY TO MARKET: A LIFECYCLE PERSPECTIVE

Preclinical | Phase I | Phase II | Phase III | Market

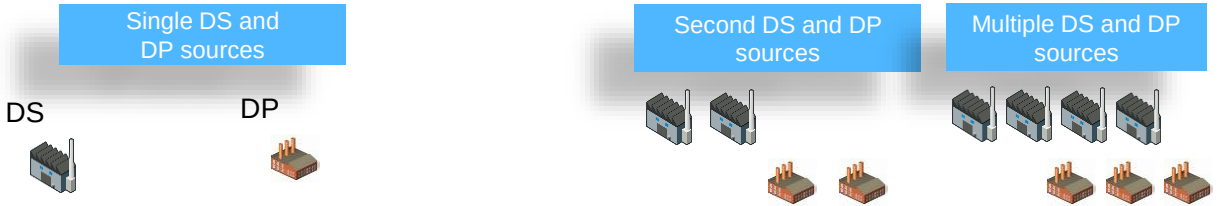
Scale changes

Pilot scale production → Small scale production → Scale-up production → Commercialized large scale production

Process changes

Platform process → Process optimization → Process «locked»; Process characterization and process validation → Process improvements

Site changes



WHY MAKE CHANGES DURING THE LIFECYCLE?

To serve all patients worldwide

- Continuously growing number of patients to be treated
- Continued development into new indications
- Need for increased production volume, compared to clinical stage

To introduce state of the art technology

- Raw-/Starting Materials
- Fermentation
- Purification
- Formulation (IV to SC)
- Configuration (vial to PFS)

Meet new regulatory requirements

- Non-animal origin
- Antibiotics-free

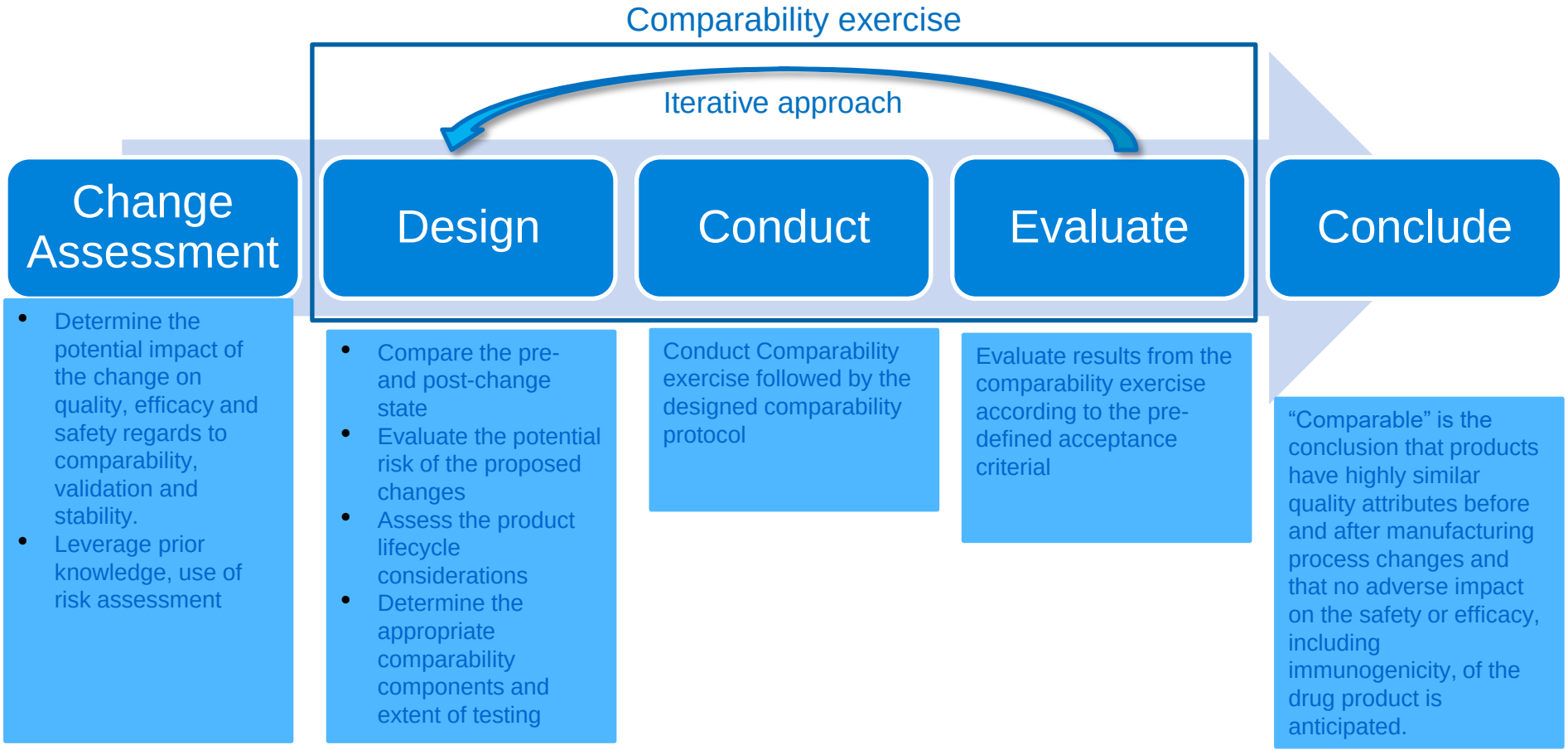
RISK-BASED COMPARABILITY IS A KEY ENABLER TO THE PRODUCT LIFECYCLE

Category	Components (as appropriate)
A	**Control System Testing** • QC batch release data, including potency • Process-related impurity levels (host cell proteins, DNA, Protein A) where applicable
B	**Extended Physicochemical and Biological Characterization** • Physicochemical characterization, for example - glycan analysis, peptide map LC/MS, DSC, FTIR, ... • Biological characterization, for example - Fc receptor interaction assays, effector function assays, assays that measure secondary MOA, SPR or other binding assays, etc. • Degradation, for example - accelerated stability, stressed stability, forced degradation

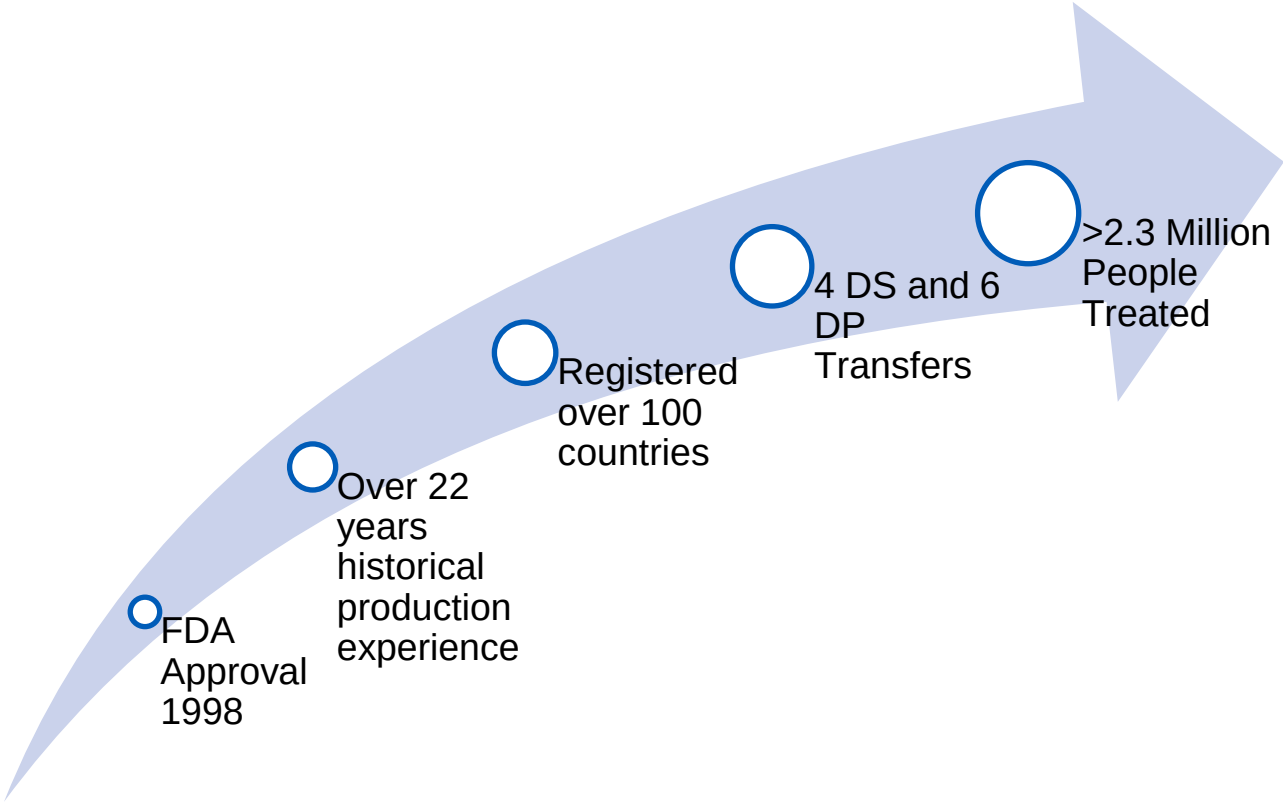
C	**Non-Clinical (*In Vivo*) Bridging**
	• Animal PK or PK/PD studies
	  ○ Rodent PK may suffice
	  ○ May need primates or other responder species for PD

D	**Clinical Bridging**
	• Randomized, dedicated PK (or PD) clinical studies, e.g. head-to-head comparison of pre- and post-change clinical material in human subjects
	• Clinical Experience
	  ○ Non-randomized PK (or PD) comparison across clinical studies
	  ○ Incorporation of the post-change material into randomized pivotal studies

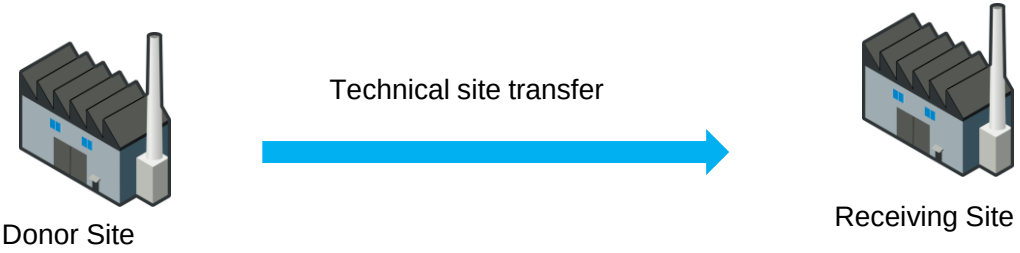
Comparability is an iterative process



CASE STUDY: MAB1 and a 20+ YEAR JOURNEY



CASE STUDY: MAB1 and a NEW DRUG SUBSTANCE MANUFACTURING FACILITY



- Comparison between the Donor Site and the Receiving Site (Gap assessments)
  - Equipment
  - Manufacturing process
  - Raw materials, reagents
  - Personal (training etc.)
- If required site specific process validation at the receiving site

Technical batches (PPQ batches) are manufactured to verify successful transfer of manufacturing procedures, equipment and material requirements, control systems and process knowledge.

Change Assessment

CASE STUDY: RISK-BASED COMPARABILITY CRITERIA

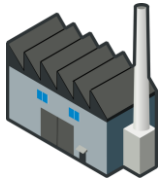
Tier	Parameter	Pre-Defined Comparability Acceptance Criteria for All Validation Batches	ICH Q5E
1	QC Release Testing	Must meet specifications	**Check for Confirms To Specifications**
2	Comparison QC Results versus Historical Data	Profiles must be comparable to controls (Qualitative) Must be within manufacturing history (Quantitative) No significant shifts of QA relative to historical	**Check for Consistency** Often Tighter than Specifications
3	Stressed Comparability Study At Elevated Temperature	Profiles and overall behavior are comparable to controls (Qualitative) Rates of change are comparable to controls (Quantitative)	**Check for Subtle Differences** might not be readily detected otherwise
4	Extended Characterization	Selected assays that are *not* on the control system but address analytically residual risks specific to change not covered by above	Check for differences that **might not be detected by control system**

Setting Acceptance Criteria

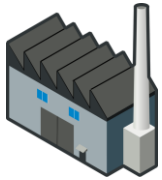
Study Design

Comparability Exercise – Roche Approach

Case Study (cont.)



Donor Site
DS1



Receiving Site
DS 2

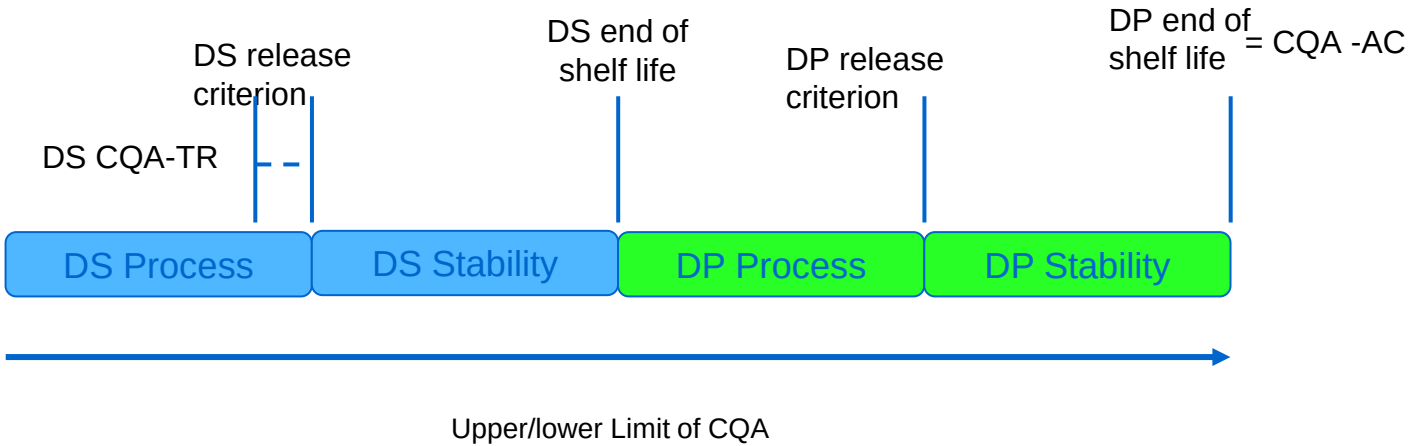
The product manufactured at DS1 is comparable to the product manufactured at DS2

Study Conclusion

Comparability – Roche Approach

Case Study: Adding a new Drug Substance manufacturing facility impact on Drug Product

Product Release and Shelf Life Specification



During a DS site transfer, the changes are made in the DS process, therefore, DS level is the most appropriate step for comparability study to evaluate potential risk to product quality.

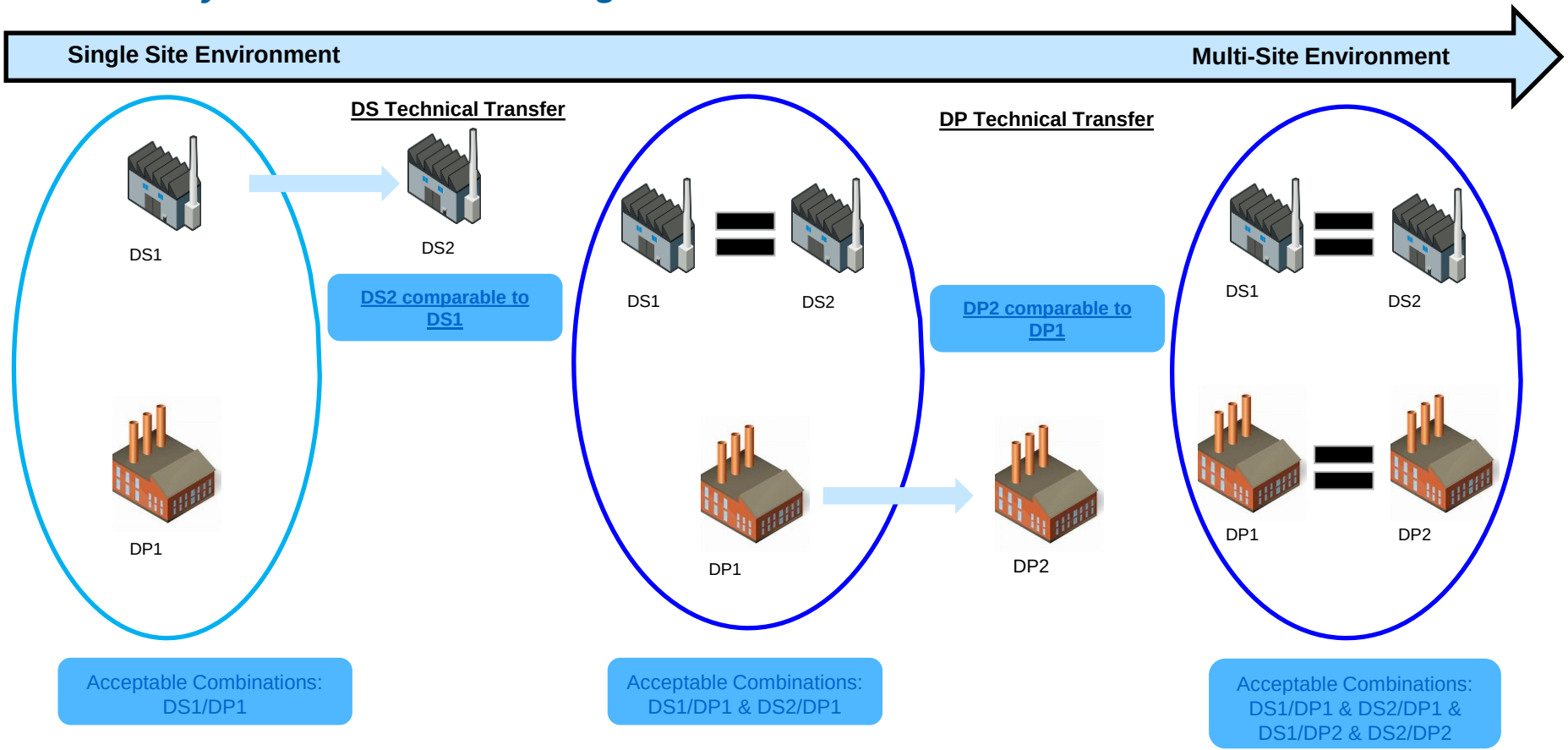
Comparability – Roche Approach

Case Study: Adding a new Drug Substance manufacturing facilty impact on Drug Product Quality

- If the comparability at DS level has been demonstrated
- If there is no DP manufacturing process change associated with DS change
- If there is no DP specification change associated with DS change
- If DP manufacturing process is validated and robust
- If the risk assessment conclude, there is no potential risk on product quality, efficacy and safety by adding a new DS manufacturing facility

Comparability – Roche Approach

Case Study: Evolution from a Single Site to Multi-Site Environment



Key Take-Aways

Risk-based comparability is an enabler for successful management of supply in a multi-national company

- Site transfers.
- Reliance on prior knowledge, risk management and understanding gaps and differences to support product quality assessments.

Post-approval changes directly support supply of life-saving medicines to patients in need

- Supply chain resilience.
- Continuous improvement of manufacturing processes.
- Complex and global networks of drug distribution and supply.

Acknowledgments

- Qiong Lin-Willitsch
- Meng Yang
- Mohan Lackshmanan
- Enda Doyle
- Brian McRee
- Dalila Bachir-Cherif
- Mark Nolden
- Jixiang Jiao
- Dana Swisher

Doing now what patients need next