Late-Stage CMC Analytical Speed Bumps: When 'Later' is Suddenly *Now*...

Dr. Nadine M. Ritter

President and Analytical Advisor

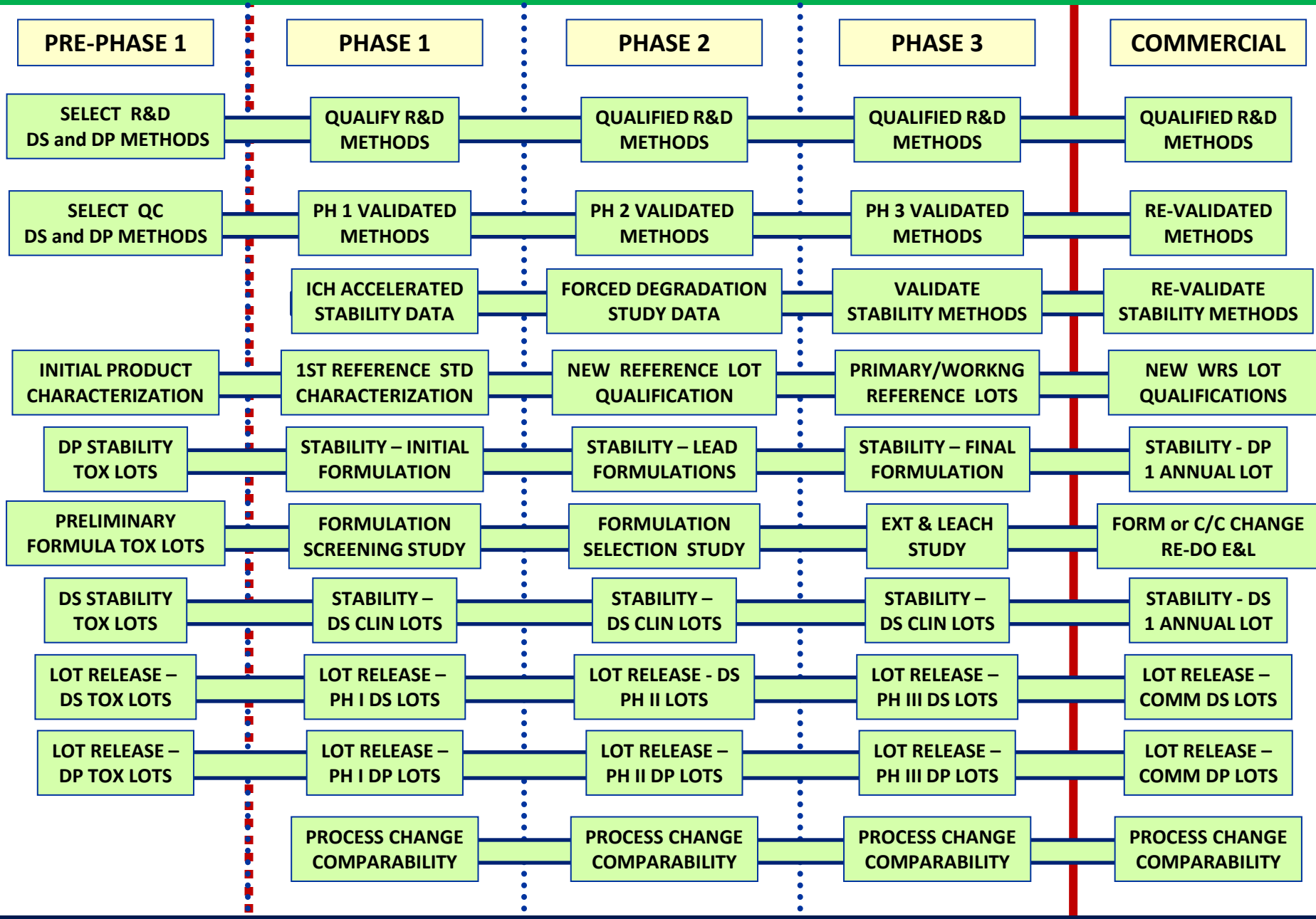
GLOBAL BIOTECH EXPERTS. LLC

Nadine.Ritter@GlobalBiotechExperts.com

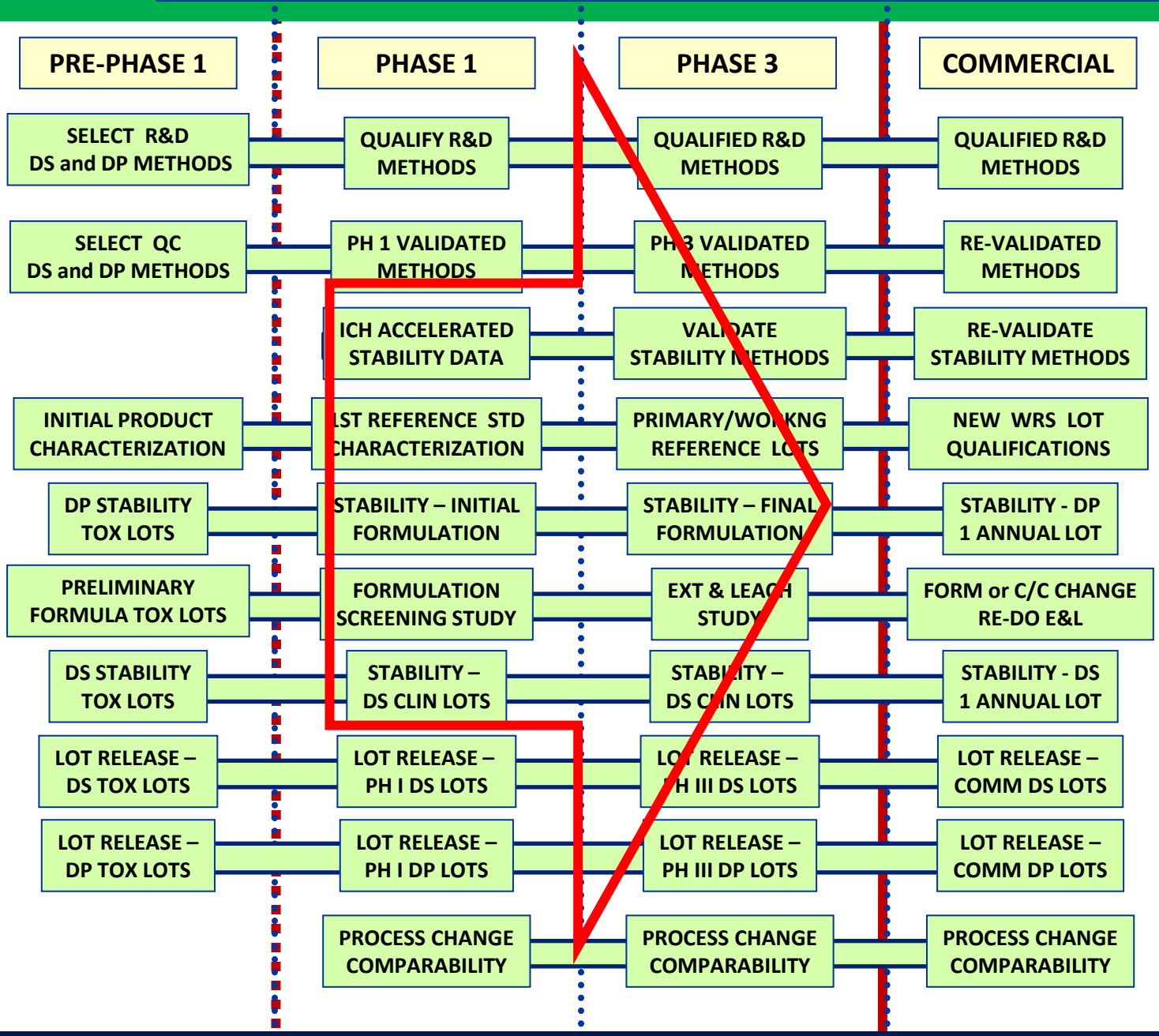
Required CMC Analytical Data Packages for Biological Products of Any Modality

1. **Compositional, Conformational and Functional Characterization** (of Active Entity(ies)
2. **Identity and Characterization of Impurities** (Product impurities/degradants; Process residuals)
3. **Establishment and Bridging of Product Reference Standards** (Interim; Primary and Working)
4. **Qualification of non-GMP Methods used for Characterization, Comparability, *Similarity*** (Establish method performance capabilities for the intended test materials)
5. **Validation/Verification of GMP Methods for Release, Stability** (Confirm method performance capabilities for the intended test materials against phase-appropriate acceptance criteria)
6. **DS and DP Batch release QC data** (History of methods, pedigree of reference standards)
7. **Formulation Development** (Excipient selection; Optimization of formulation/presentation)
8. **Extractable and Leachable Studies** (Confirmation for DP in vial/matrix; Risk assessment DS)
9. **Degradation evaluation** (Establish stability profile, validate stability methods, characterize structure/function; characterize degradants, assess product comparability, bridge test methods)
10. **ICH Stability data** (real time target, accelerated, stress conditions; initial assessment of stability methods; assess comparability of deg rates; history of methods and pedigree of reference standards)
11. **DS and DP Comparability Studies** (Process changes: Scale, Site, US/DS steps, Form/fill steps)
12. ***Biosimilar Analytical Similarity*** *(Physical/Functional Characterization of RLD; Comparison of RLD and BSP)*

KEY ANALYTICAL CMC DATA SETS: TYPICAL CLINICAL TIMELINES



KEY ANALYTICAL CMC DATA SETS: ACCELERATED PROGRAMS



Shortened Clinical Timelines
****SQUEEZE****
CMC STUDIES and
****MAGNIFY****
BAD CMC DECISIONS

CRITICAL
CMC ANALYTICAL GAPS
WITH BIOLOGICAL PRODUCTS

Chronic Analytical CMC 'Hot Buttons' for Biologics

- Inadequate experimental characterization of process design space and process robustness (sampling points, types of methods, amount of data) to support process QbD, PPQ and CPV claims *ATMPs: Total control strategy highly dependent on process elements to offset limited end-product testing*

- Inadequate analytical comparability protocols to assess impact of process changes (too few parameters, acceptance criteria too wide); inadequate data to validate comparability of small-scale models (SSM) for process development studies *ATMPs and BSP: More heavily leverage SSM for process QbD and robustness data*

- Failure to consider long-term impact of first Interim Product Reference Standard; inadequate calibration of potency Reference Standard; inadequate analytical bridging and stability studies for reference standards; deficient protocols for two-tiered Primary and Working Ref Stds *ATMPs: Reference standards are even more challenging (highly labile) for final product; increased pressure on Ref Stds for intermediate materials*

Chronic Analytical CMC 'Hot Buttons' for Biologics

- Misunderstanding multiplex nature of Host Cell Proteins (HCPs); insufficient assessment of HCP immunoreagents, reference standards, and assay controls; inadequate / incomplete validation of HCP ELISAs; misunderstanding of quantitative HCP mass spec; insufficient characterization and comparability of HCPs; *ATMPs: Residual HCPs less risky due to dose regime, but still critical to process control and consistency, especially of intermediate materials*

- Insufficient characterization and quantitation of endogenous subvisible particulates in protein solutions; lack of a semi-quantitative QC visual particle test for appearance specifications ('essentially free of translucent particles') *ATMPs: SVP/VP less risk to do dosing regime, but still critical to process control and consistency, especially of intermediate materials*

- Inadequate data sets on extractables from process/product contact materials; incomplete leachate studies under real-time process/product conditions *ATMPs: leachables less risk to do dosing regime, but still critical to process control and consistency, especially of intermediate materials*

Chronic Analytical CMC 'Hot Buttons' for Biologics

- Lack of sufficient orthogonal analytical methods that are 'stability-indicating'; inadequate experimental establishment of the product stability profile; lack of adequately systematic, comprehensive forced degradation studies to support method validation, method tech transfer, method bridging, and comparability protocols *All biologics: Cannot claim product is stable without proof that all potential degradation pathways are detectable; degree of deg is a spec issue*

- Insufficiently phase-appropriate validation GMP analytical methods; failure to validate both working range and reportable range (especially with in vitro bioassays); improperly designed repeatability experiments for method intra-assay replicates; inadequate rigor of intermediate precision runs for full GMP; missing data to confirm stability-indicating methods; missing data confirming robustness of key procedural steps *(especially sample preparation and handling) ATMPs: New analytical technologies just beginning to be used in GMP conditions*

- Platform method validations with inadequate product-specific validation data; lack of access to CRO generic platform validation data *All biologics: All supportive validation data must be provided for each product for GMP; might leverage robustness optimization data across products, but must confirm robustness of key method steps*

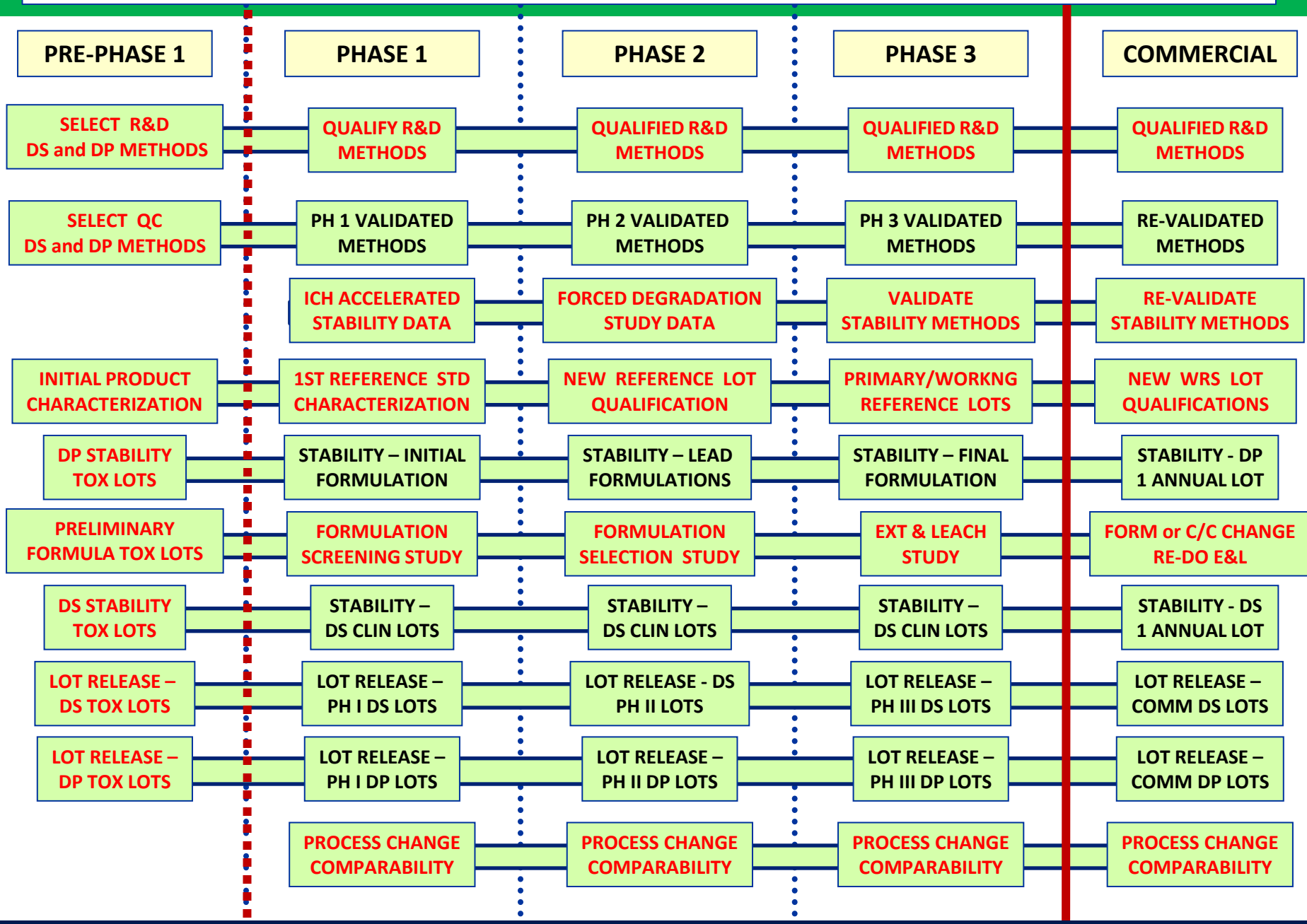
Chronic Analytical CMC 'Hot Buttons' for Biologics

- Inadequately detailed method SOPs to assure consistent reliable QC method performance; lack of control of critical assay reagents; lack of adequate, meaningful method system suitability measures; lack of tracking/trending validated method invalid rates to confirm operational state of control *ATMPs: Many new methods are highly complex, therefore need even more control over procedure to assure consistent, reliable results (especially sample preparation and handling)*

- Data integrity for GMP laboratories (beyond Part 11); data integrity for supportive CMC studies (non-GMP studies that generate critical data for project and regulatory decisions) *ATMPs: Still very close to academic origins, especially for early clinical phases; cellular materials 'practice of medicine' GCP is different from GMP*

- Poor / inconsistent quality practices in academic and R&D labs; limited control and consistency of the analytical methods used for characterization, comparability or biosimilarity studies in non-GMP laboratories; no evidence of 'fit for purpose' studies to establish method performance (method qualification); incomplete / untraceable data and documentation of R&D studies *All biological products: Use of R&D data for training and tuning AI models*

KEY ANALYTICAL CMC DATA SETS: NON-GMP R&D DATA



CMC R&D Data Integrity Failures Cast Grave Doubt on the Accuracy and Authenticity of Other Critical R&D Data

FDA STATEMENT

Statement on data accuracy issues with recently approved gene therapy

FDA U.S. FOOD & DRUG ADMINISTRATION

For Immediate Release: August 06, 2019

Statement From: Director - Center for Biologics Evaluation and Research (CBER)
Dr. Peter Marks M.D., PhD.

"It is the manufacturer's responsibility to submit complete and accurate information in marketing applications for evaluation by the FDA."

"Ensuring truthful, complete and accurate data in product applications is a critical component of industry's responsibility as they work to demonstrate the safety, purity, and potency of biological products."

"The submission of such truthful, complete and accurate data is also critical for the FDA to be able to protect the public health, and the law requires it."

FDA Guidance: Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products (Jan 2026 draft)

The data used to develop the AI model should be fit for use, which means the data should be both relevant (e.g., includes key data elements and sufficient number of representative participants or sufficient data that is representative of the manufacturing process or operation) and reliable (i.e., accurate, complete, and traceable).

How Reliable are R&D Data Used for Training and Tuning AI CMC Models?

- *What are the sources of the CMC data that are incorporated into the AI training databases used to support regulatory decision making?*
- *Who is independently verifying that each of these AI data sets are sufficient accurate, reliable, and traceable?*
- *What are they specifically looking for in their review of AI training and tuning data integrity?*
- *How is this verification process documented for each of the AI data sets?*
- *What checks and balances are in place to catch erroneous or incomplete data sets before they are incorporated into AI models?*
- *What are appropriate CAPAs if AI data sets are later found to be inaccurate?*

Quality Risk Management and Data Integrity in R&D Laboratories Supporting CMC Lifecycle of Biological Products

Journal of Pharm Sci 113 (2024) 3123–3136

Brent S. Kendrick, John P. Gabrielson, Deanna Hunt, Merry Christie, Steven Bowen, Christina Vessely, Richard S. Rogers, Chad Cleveland, Karl Maluf, Shawn Roach, Nadine Ritter

Making sound strategic CMC decisions under any circumstances assumes data from R&D studies are reliable, traceable, and complete.

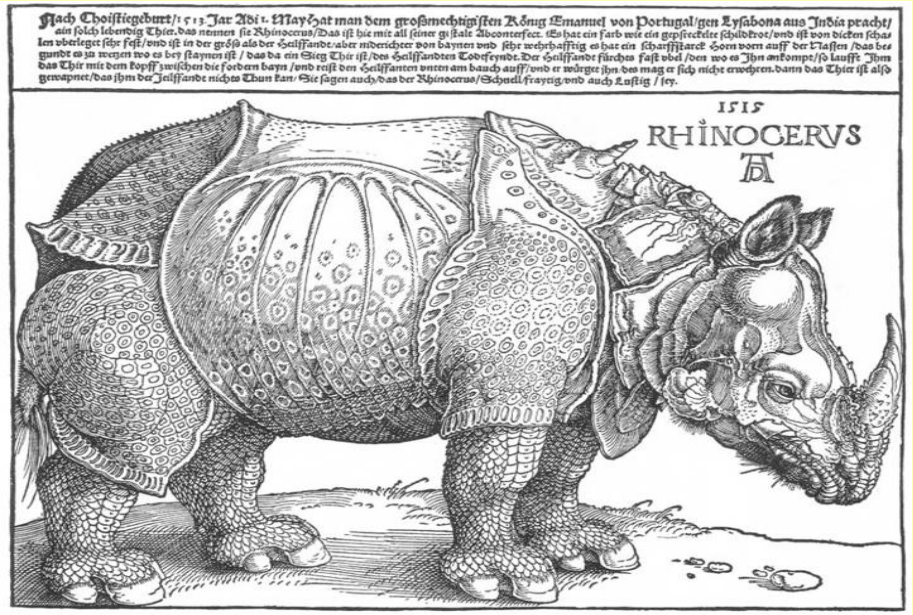
While there are specific regulatory guidelines on phase-appropriate cGMP activities, none exist for quality practices in R&D CMC laboratories conducting non-cGMP studies.

Hindsight is not the time to discover that R&D studies lack key elements that would otherwise have allowed the data to be directly presented to regulators, if needed.

There is a strong prospective business interest in protecting considerable investments made for CMC R&D studies.

Therefore, establishment of a robust and stage-appropriate R&D laboratory quality system is essential for companies seeking to capitalize on prior knowledge, protect investments, and be prepared for accelerated approval pathways.

THANK YOU!



www.GlobalBiotechExperts.com