Application of Phase-Appropriate CGMP and Quality Systems to the Development of Protein Bulk Drug Substance (or API)

PDA Task Force

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- **Personal thanks to Daniel Bollag, Sr. VP RA & Quality at ARIAD Pharmaceuticals for his continued support and encouragement**

Task Force Strategy

- To bring together subject matter experts representing:
  - Industry: Small and Large Companies
  - Consultants: Experts in their field
  - Regulatory Agencies
- Get input and comments from US, EU and Japan
- Get input and comments from academic facilities involved in GMP activities

Overview

- **The Technical report's goal is to propose a basic, science-based and compliant approach towards the development of Protein Bulk Drug Substance (API)**
- **Its scope covers the development path from R&D, through preclinical studies, through PD and scale up to commercialization**
- **It describes the minimum activities and systems considered appropriate that should support effective GxP (GRP, GLP, GMP, etc.)**

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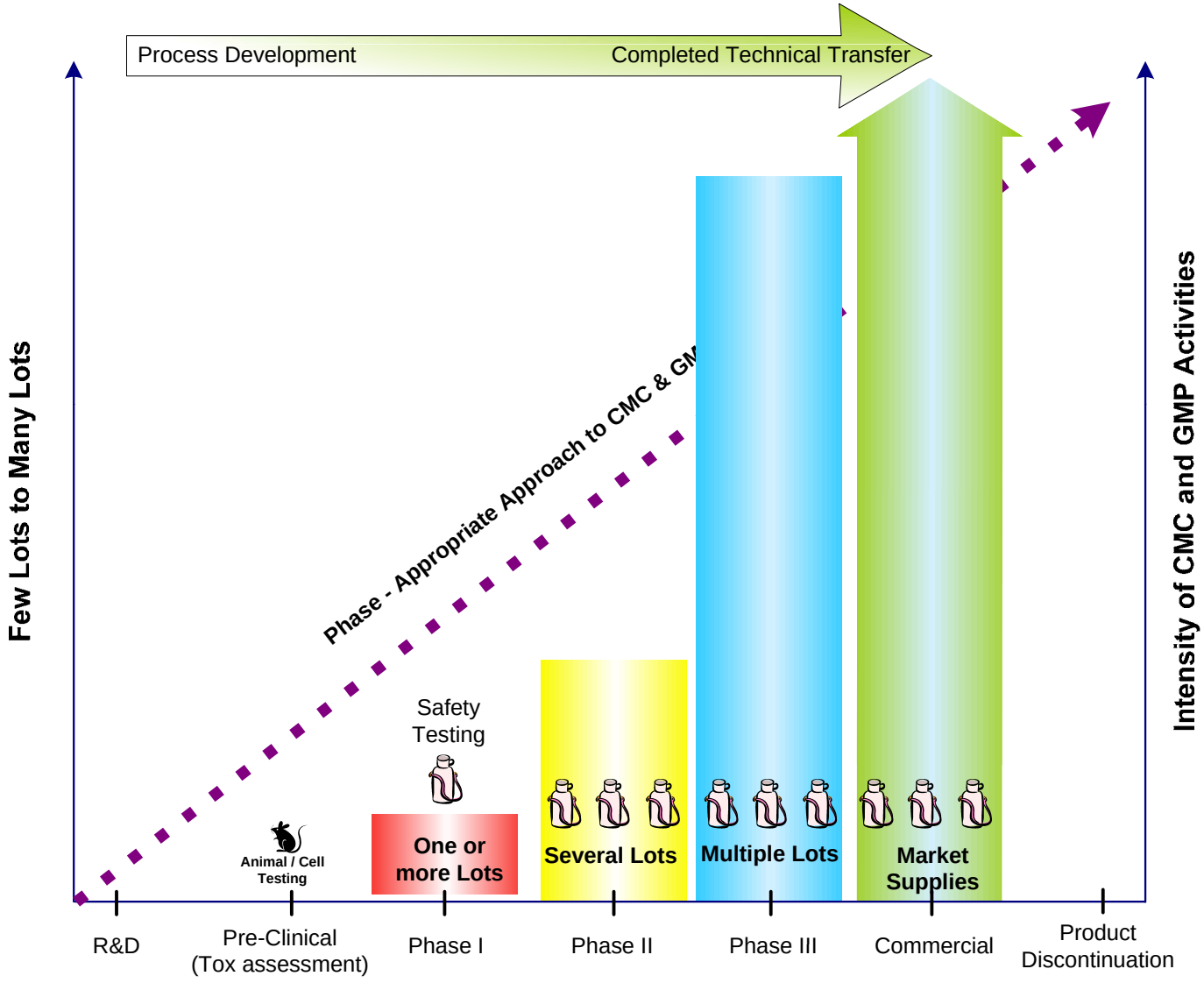
Scope

- The scope of this technical report covers phase-appropriate Current Good Manufacturing Practices (CGMP) during therapeutic bulk protein drug substance manufacturing from the R&D stage through completion of phase 3 clinical trials
- The scope also includes implementation of a pharmaceutical quality system that ensures the safety and quality of products intended for use in clinical trials.
- This report will focus on current best practices and the appropriate regulatory framework.
- Chemistry and Manufacturing Controls (CMC) submission/dossier requirements for therapeutic proteins at the pre-marketing phase are **not within the scope** of this document

Purpose

- To define CGMP principles important for manufacturing pre-marketing therapeutic bulk protein, providing examples of approaches towards CGMP compliance during clinical studies
- The examples provide an overview of the expectations across regulatory authorities as products proceed from R&D to completion of phase 3 clinical trials
- The report illustrates a phase-appropriate approach to the implementation of CGMP, enabling supply of safe clinical materials while maintaining manufacturing flexibility at non-commercial scales & during scale up & process transfer
- The report also describes a basic framework for clinical trial manufacturing for sites where commercial manufacturing is not the organizational goal (e.g. university clinical investigators, start-up biotech firms).
- This report is **not intended** to serve as a regulatory guidance.

The Bulk Drug Substance Development Life Cycle



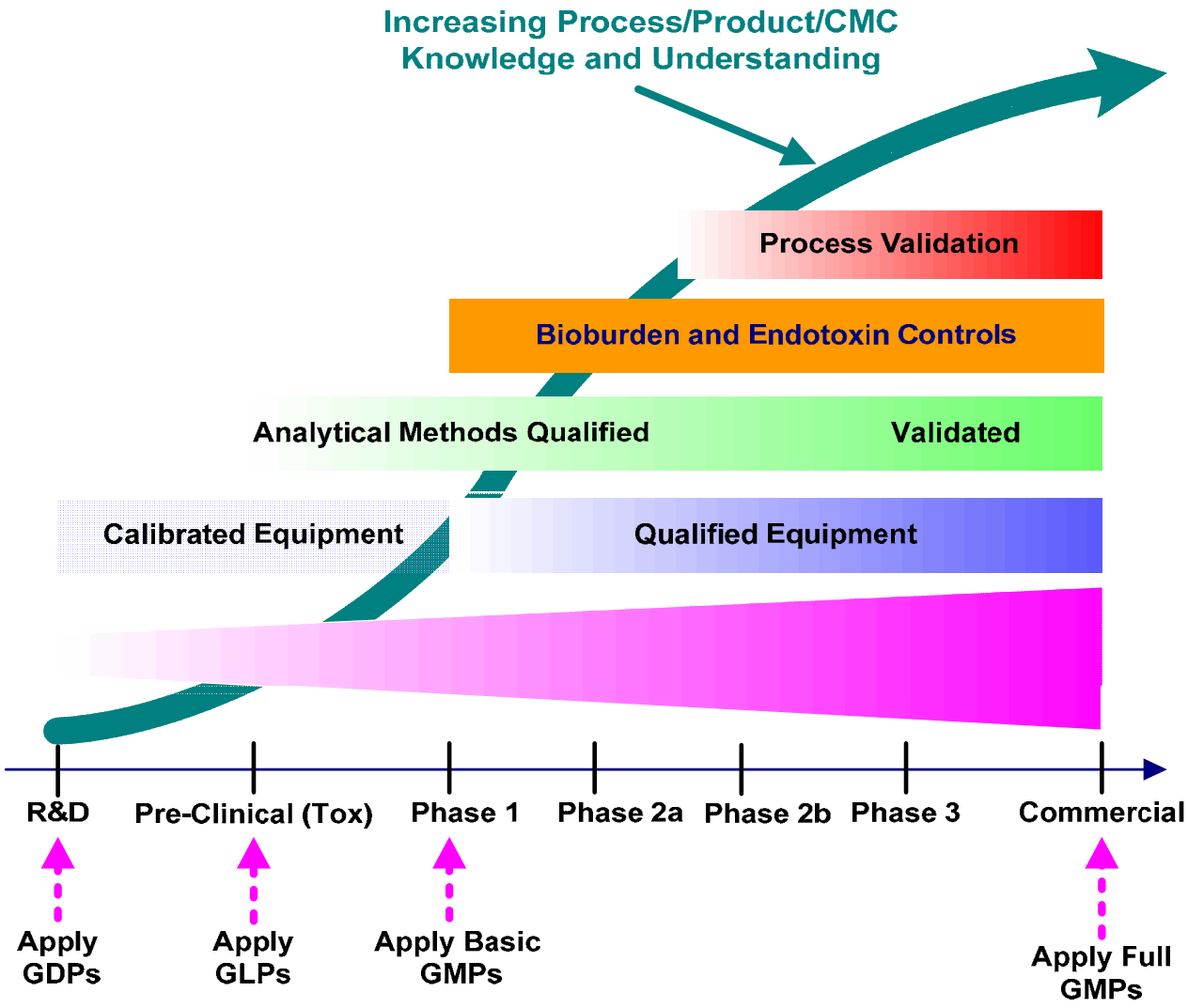
*Size of study is often dependant on disease state, e.g. oncology vs. endocrine

Quality and Compliance expectations increase along the Drug Development timeline

- **R&D / Phase I / Phase II / Phase III / Pre - Commercialization**
- **Quality / GMP expectations for Biotech Bulk Drug Substance applied by Phase of development**
- **Good Research and Documentation Practices**
- **GLPs Pre-Clinical (Tox assessment)**
- **Early Phase cGMP expectations**
- **Bioburden and endotoxin control**
- **Calibrated equipment / Qualified equipment**
- **Qualified Methods / Validated Methods**
- **Process validation**
- **Pre-Commercialization cGMP expectations**
- **Process Understanding increasing - QbD**
- **Risk-Based/Science-Based Approach to compliance decisions ICH Q8/Q9/Q10**

A Risk-based approach:

Increased Application of GMP and Quality Systems



Product Quality and the relationship between GMPs and CMC requirements/expectations

- The regulatory strategy used to ensure biopharmaceutical product quality involves both CMC and CGMP oversight.
- CMC requirements set the criteria and controls for manufacturing and testing, as described in the submission or dossier.
- CGMP requirements are derived from the regulations and guidelines pertaining to the implementation of practices and standards in a manufacturing facility that allows for the consistent production of a quality product with the intended purity, safety and potency characteristics

Example of table from the Technical Report

4.0 CGMP AND QUALITY SYSTEM RECOMMENDATIONS BY STAGE OF DEVELOPMENT

System	R & D	Toxicology	Phase 1 [a, b, c]	Phase 2 [a, c]	Phase 3 [c]
QUALITY: • Quality management/ oversight • personnel training • documentation &records • change management • deviations/investigations • CAPA • Auditing • quality agreements	Personnel have science background & are trained in routine lab practices. Signed notebook records are kept of production and testing activities. If batches fail, they are studied to increase product and process knowledge. R&D activities are well documented in the notebooks, as well as in periodic development reports.	GLP practices are implemented as per regulations in specific global regions EU and FDA GLP Requirements cover the areas of: • Organization and Personnel • Facilities • Equipment • Facility Operation • Articles • Protocol and Conduct • Records and Reports • Disqualification It is expected that a Lab director with a science background is in charge of the Quality Unit, and reviews all procedures and	Responsibilities are governed by CGMP (e.g., ICH Q7 and Annex 13). QA/QP involvement may increase by phase of development for some items (e.g., as methods are fully validated or transferred, as master batch records are created). QA/QP responsibilities must not be delegate to another functional area, but may be contracted to independent bodies. Quality standards (e.g., policies, SOPs) must be reviewed and approved by QA and be subject to periodic review. . It is recommended that for each phase of clinical development, the relevant summary development reports should be completed to review process development activities and results. The reports should include an evaluation of deviations and unexpected results that are encountered during clinical production, scale up, tech transfer, characterization studies, etc. The Bulk Drug Substance is released by QA/QP after review of the completed batch record, COA, environmental and water monitoring data, deviations and changes, the investigational new drug registration (e.g., IND, IMPD), and any other relevant information available in the product specification file as specified in the procedures for batch release. QA/QP can delegate the release of manufactured intermediates to other qualified personnel upon formalized agreements and acceptance. For Phase 1 generic batch records may be used. As clinical development proceeds, more detailed batch records with acceptance criteria or target values should be developed. Master batch records should be used prior to conducting process validation. Deviations should be recorded in the batch records. Deviation and investigations are increasingly thorough as clinical development proceeds. By phase 3 a formal deviation tracking system and a CAPA system should be in place. Clinical materials should not be distributed to the clinical supply chain until all open deviations, test results, or other documentation are closed and approved by QA/QP.		

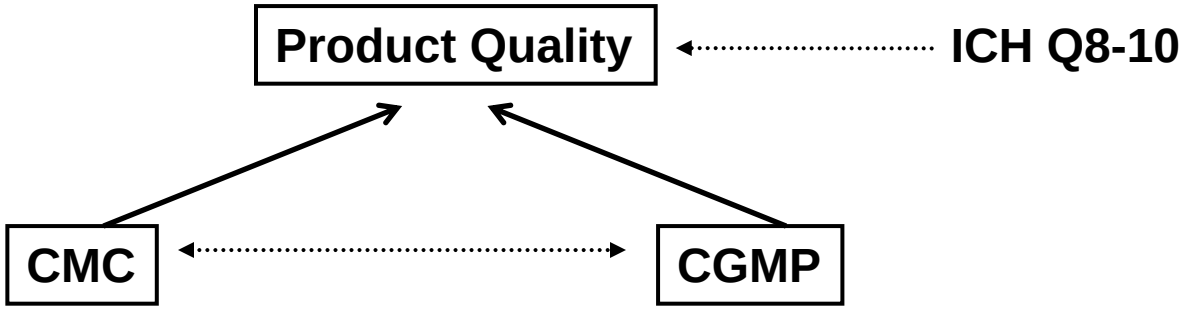
Example of table from the Technical Report (2)

System	R & D	Toxicology	Phase 1 [a, b, c]	Phase 2 [a, c]	Phase 3 [c]
	samples are tracked in logbooks.		current process knowledge and this will continue throughout phase 3.		
LABORATORY: • General controls • testing intermediates and bulk • validation of analytical methods • expiry and retest dating • reserve and retention samples	Quality by Design Principles should be applied to the selection, development and qualification of appropriate assays Expiry and storage of assay reagents can be set as per vendor recommendations. Reserve samples should be sufficient to bridge equivalency to subsequent batches.	Testing as per R & D, but includes tests for attributes that can confound animal testing (e.g. such as contaminant and impurities that may generate erroneous results: MAP/HAP and LAL).	Lot, in-process and stability testing as per regulatory dossier is implemented. OOS results are investigated with QA/QP involvement focusing on root cause. Analytical instrumentation calibrated and on a suitable PM schedule. Vendor equipment packages demonstrate that scientifically sound results are produced. System suitability tests are advised to be part of the testing methods. Initial method qualification for most assays should be initiated; safety-critical assays may need to be validated (e.g. sterility, virus). Lab equipment, balances and pipettes should be routinely calibrated on a PM schedule. Expiry and storage of assay reagents is set as per vendor	Same as phase 1, but method qualification at a more advanced stage	Lot, in-process and stability testing as per regulatory dossier is implemented. OOS investigation should comply with out of specification regulatory requirements for the appropriate global region(s). Analytical assay validation activities should be at an advanced stage or complete (before registration stability lost are manufactured) lots). Lab equipment, balances and pipettes should be routinely calibrated on a PM schedule. Complex analytical equipment may need to be qualified. Expiry and storage of assay reagents and samples is set as per vendor recommendations, scientific knowledge and/or experimental data. Reserve samples are sufficient to bridge equivalency to subsequent batches. Assays procedures and results are recorded in analytical batch records or a LIMS system; samples, reagents, calibrations and key supplies are tracked in logbooks. Analytical batch records and logbooks are reviewed by

Overlap Between GMPs and CMC

- Because they are both critical pillars of product quality, there are often areas of overlap between CMC considerations and GMPs.
- Examples of areas of overlap include:
  - process development
  - Validation
  - continuous process improvement.
- Resolution of the overlap can be achieved by viewing CMC development as a “process, criteria and controls setting activity” and GMPs as an “implementation activity”

The Synergy of CGMP and CMC



Focus:	**Submission/dossier**	**Facility/Manufacturing/Testing**
Industry Role:	**Setting manufacturing and quality criteria and controls**	**Implementing manufacturing and testing practices designed to meet manufacturing and quality standards**
Guidance:	**ICH Q1-6**	**ICH Q7**
Agency Role:	**Assessment and approval of manufacturing and quality standards and controls**	**Verification of conformance to CGMP and to regulatory submission/dossier standards through facility inspections; evaluation of quality system**

Note: For Biotechnological products, process validation summary data is included in the regulatory application. Validation data and conformance to the commitments and standards described in the Marketing Application are verified on site inspection.

Progress Status

- Comments incorporated from PDA membership and the Biotechnology Advisor Board in mid - 2010
- Draft version completed November 2010
- Sent out for comment by EMA and CBER representatives
- Next Steps:
  - Comment by academic/”small” GMP manufacturers
  - Review by PDA Japan
  - Review and Approval by PDA Biotechnology Advisory Board.

QUESTIONS?