Failing to plan is planning to fail: the case for early use of cGMP raw materials

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Insufficient planning, in the early stages of scale-up, results in an inefficient process at best, or validation failures leading to serious market delays at worst. Using cGMP grade reagents earlier in the transition to large-scale commercial manufacturing makes for a seamless transition — maintaining quality and viability while avoiding additional costs, potential process redevelopment and lost production time.

When you identify suppliers of higher quality reagents ahead of time — chemicals that have been extensively tested and documented — you gain heightened supply chain security and assurance of regulatory compliance. Use cGMP raw materials during development to:

- Minimize risk of contamination or aberrant results due to impurities
- Provide material traceability to support regulatory compliance
- Eliminate requalification of material due to unavailable grade and quantity of material after transfer
- Ensure product consistency that meets intended specifications

Current Good Manufacturing Practice (cGMP) regulations are set regionally, based on guidelines developed by organizations including the International Conference on Harmonization (ICH), Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme (PIC/S), and regulatory agencies. They focus on preventing cross contamination and keeping environmental contaminants out of the product, thereby simultaneously protecting the end user and the product. There is no cGMP certification; they are standards to maintain quality and purity characteristics in pharmaceutical development.

Quality: Industrial and lab-grade reagents do not guarantee critical performance specifications

The reagents needed for clinical manufacturing must meet additional regulatory and testing requirements to validate sterility, consistency and efficacy. This includes more quality control testing of initial raw materials, more in-depth documentation to show manufacturing control and validated manufacturing and cleaning processes to minimize risk of product failure and subsequently, patient safety concerns due to variability or contamination.

KEY CHALLENGES

- **Lot release testing**
  Research use only (RUO) raw materials (and equipment) do not include comprehensive — and time-consuming — QC testing, specifically for endotoxins and particulates leading to patient safety concerns
- **Sterility validation**
  With the change to cGMP products, this is not a 'one and done' test validation; dose audits must be done regularly to prove sterility
- **Clinical comparability studies**
  Time-consuming clinical comparability studies to prove the raw material changes do not alter the final product. By making the change early, you get less chance of variants or atypicals and that validation will fail

WHAT WE OFFER

- Regulatory and quality systems and history of supporting customers with regulatory submissions
- Quality audits with Rx-360 available to license
- Certified ISO 9001 and ISO 13485 quality systems
- Animal origin-free or EMA/410/01 compliant materials
- Sterility validation per ANSI/AAMI/ISO 11137 (VDmax25)
- Sterile barrier shelf-life validation per ANSI/AAMI/ISO 11607
- BPOG standardized extractables testing protocol
- Endotoxin USP <85> and particulate USP <788> lot release testing
- Lot-to-lot consistency and comprehensive supportive testing
- Custom specifications and performance characteristics available

Documentation: Lack of documentation support can lead to delays or rejections

Documentation serves as a record that a supplier's manufacturing facility, processes, and operators are fully qualified. It is not a box to be checked, but should be a systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components (ICH Q10).

KEY CHALLENGES

- **Process validation**
  Supporting documentation should be in place for scale-up. If you wait, you lose time in getting necessary documentation
- **Traceability**
  Raw materials at this level must be documented and traceable. This ensures any issues with end product or process can be adequately investigated and ruled out
- **Certified quality systems**
  Documentation is not a stand-alone deliverable. These change with the transition from RUO to cGMP, as do corrective/preventative actions and documentation requirements

WHAT WE OFFER

- Certificates of Conformance, Quality or Analysis are available with SDS documents online
- Equipment Cleaning and Use Record
- Records of Raw Materials, Intermediates, API Labeling and Packaging Materials
- Master Production Instructions (Master Production and Control Records)
- Batch Production Records (Batch Production and Control Records) and Review); our knowledge of regional differences facilitate regulatory compliance
- Laboratory Control Records
- Supply chain statements
- Rigorous documentation of deviations along with root cause analysis and corrective/preventative actions

Supply: Reagents that are unavailable cause disruptive changes and/or stockouts

Collaborative planning, smart forecasting and sales and operation planning are needed to keep your cGMP materials in stock to hit your manufacturing goals. Establishing a comprehensive supply chain strategy, as well as a robust management of change program, as early as possible mitigates risk.

KEY CHALLENGES

- **Change management**
  Change controls become burdensome in full cGMP systems; materials that worked for one workflow may not work for another
- **Limited raw materials list**
  Key to build a diverse and large approved raw material parts list ahead of time, so a stable supply chain is in place with qualified secondary suppliers in case a reagent is discontinued
- **New production/distribution sites**
  Moving manufacturing can disrupt a previously secure supply of cGMP reagents; facilities must be certified. Changing the source of supply of critical raw materials requires adherence to formal change control system
- **Supplier auditing**
  A system for evaluating suppliers of critical materials as necessary; all cGMP production materials must be traceable

WHAT WE OFFER

- Collaborative planning, forecasting and replenishment (CPFR): we provide service level reports on assurance of supply through our Critical Materials Care team
- A formal Management of Change (MOC) program and change notification services for supply consistency and transparency
- Certified global cGMP and cGDP facilities; with local field-based support on three continents
- Supplier auditing and integrity provides proactive, risk-based audits that enable us to understand the capabilities of new suppliers and collaborate effectively to promptly address CAPA if needed
- Large portfolio of quality premium products and chemicals

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Beth Kroeger-Fahnestock is a Director, New Product Introduction, in Avantor's Biopharma Production division. She currently manages new product launches to support Avantor's mission in bringing lifesaving medicines to market. She has extensive industry experience in Manufacturing, Validation, Technical Transfer, R&D, Compliance, and Quality from her various positions she has held. Her areas of expertise include large-scale Bioprocess systems, downstream purification operations, and process and cleaning validation along with cleanroom environmental control, speaking frequently on these topics for educational and professional organizations. She served on the ISPE task force responsible for writing the ISPE Guidance: Cleaning Validation Lifecycle – Applications, Methods, and Controls Good Practice Guide, published in 2020 and was an Adjunct Lecturer, Temple University, School of Pharmacy, RA/QA Graduate Program for several years. She earned a B.S. in Biochemistry from the University of Missouri, St. Louis.

Why choose Avantor®?

Trust chemicals and excipients from Avantor® to help you reach the market faster with new biologics. With our global network of cGMP and cGDP manufacturing facilities, customer-centric quality programs, comprehensive management of change system and in-depth industry expertise, Avantor® can help you improve your production process performance, increase product yield and comply with regulatory requirements.

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