

# Integrating Good Manufacturing Practices During the Transition from Clinical Trials to Commercial Manufacturing

By Mark Zemler

## Executive Summary

In support of our customers, this whitepaper is sponsored by CDC Software to broaden the knowledge of regulatory issues as they relate to bio/pharmaceutical and API clinical trials and manufacturing.

Our experience shows that early adoption of GMP (Good Manufacturing Practices) by a company, can lead to a faster, lower-cost ramp-up from clinical trials to full commercial manufacturing, in-house or out-sourced. The interpretation of compliance regulations, and subsequent recommendations in this document, are a compilation of years of experience and best practices from leading bio/pharmaceutical companies.

CDC Software provides cGxP compliant transaction processing and work flow for materials management, manufacturing, financials and the extended life science material supply chain. Our systems facilitate faster, lower cost approvals and reduction of risk through improved compliance.

## Introduction

In support of our customers, this whitepaper is sponsored by CDC Software to broaden the knowledge of regulatory issues as they relate to bio/pharmaceutical and API clinical trials and manufacturing.

Our experience shows that early adoption of GMP (Good Manufacturing Practices) by a company, can lead to a faster, lower-cost ramp-up from clinical trials to full commercial manufacturing, in-house or out-sourced. The interpretation of compliance regulations, and subsequent recommendations in this document, are a compilation of years of experience and best practices from leading bio/pharmaceutical companies.

The author, Mark Zemler, has spent his 25 year career employed in various fields and functions of pharmaceutical, biologic, and biopharmaceutical manufacturing. He has contributed to Quality Control and Quality Assurance operations related to environmental monitoring, validation of sterilization processes, clean room standards and management, as well as process development and improvements. His responsibilities have included the implementation and management of microbiological quality programs for intermediate and final product and raw material testing, qualification of new methods, environmental monitoring support, and new facility validation. Most recently, Mr. Zemler has been responsible for the development, implementation and management of quality systems at early stage clinical manufacturing facilities, which served as the testing ground for the concepts in this white paper.

## About CDC Software

CDC Software's Ross Enterprise suite provides cGxP compliant transaction processing and workflow for materials management, manufacturing, financials and the extended life science material supply chain. Our systems facilitate faster, lower cost approvals and reduction of risk through improved compliance. For more information, please visit our website at [www.rossinc.com](http://www.rossinc.com).

## Integrating Good Manufacturing Practices During the Transition from Clinical Trials to Commercial Manufacturing

How does one determine whether GMPs (Good Manufacturing Practices) are required or how much GMP is necessary for the development and manufacture of clinical trial materials? There are expectations, guidance, and requirements for the actual manufacture of investigational drug products for human use, but, there are also some specific considerations regarding the rigor and robustness of the quality elements applied at these early stages.

From a regulatory perspective, it is apparent that there really is a requirement that drives the application of Good Manufacturing Practices to all phases of clinical material manufacturing intended for human or animal use. From a business perspective, early adoption of GMP by a company, can lead to a faster, lower-cost ramp-up from clinical trials to full commercial manufacturing.

The degree of application of GMP and the ease of implementation can often be linked to the maturity of the company and their related quality systems. Companies that already have the quality infrastructure in place to support registered products usually apply the same standards for the manufacture and testing of clinical trial materials as they would for marketed products. Quality Systems such as raw material receipt, testing, and release, documentation systems, validation and change control are already integrated and in use. The same can be said for CMOs (Contract Manufacturing Organizations). As CMOs serve many clients in many stages of Clinical Development, they are expected to conform to higher standards of GMP.

The elements of this discussion are most applicable to those companies that are not operating under the umbrella of a matured organization with well developed quality systems. When the company is young and the quality systems are not well developed, the requirement for GMP is often debated as to its relevance. Small companies have limited resources, both financial and personnel, and most of those resources are focused on manufacturing and development, not necessarily quality assurance and quality systems. Often times, when building the organization, the quality and regulatory departments are the last to be staffed. The limited resources, in combination with a perception of low risk for regulatory accountability lead to a less than adequate level of conformance to the GMPs.

How does one determine whether to apply GLP (Good Laboratory Practices) or GMP to a particular phase of development or manufacturing? Often this is a management/leadership issue. The Quality philosophy must start at the top and trickle down. Good Manufacturing Practices are not just limited to manufacturing operations. The relevance is driven by where and how the material is used (for instance, in an animal study or in a human study). GLP is applied to the execution of non-clinical studies, most commonly animal studies. Elements of GLP are also applied to studies that are not directly related to product manufacturing, but rather support an application, such as viral safety testing. At the basic level, the elements of GLP and GMP are the same. These are good documentation practices, control of your equipment, and the reliability and legitimacy of the data that is generated. Good Manufacturing Practices are applied to the manufacture and testing of materials used in humans. This means any material that is destined for use in human subjects. It also means any element of manufacturing this material, such as QC testing, QA release, development and qualification of analytical assays and the expected infrastructure that supports all the activities that occurs in between.

The requirements for GxP may have seemed fuzzy in the past. For companies that only do clinical trials in the United States, the FDA (US Food and Drug Administration) is not specifically involved with the development and manufacturing process for these clinical trial materials. They are more interested in the science behind the product, not whether adequate control for safety and quality are in place. Because of this distance between regulator and manufacturer, the requirement tends to become diluted. The decision to apply Quality Practices, and the degree of application, are driven by several other factors relevant to the stage of development. The closer to actual registration of the drug product, the more attention paid to the integration of GMP into the processes. At the early stages, the distance from an actual inspection and the review of practices can lead to minimal application of quality systems. However, for those companies that might perform trials in Europe for instance, there is a high probability of an inspection for purposes of GMP Certification.

A company must exercise due diligence, regardless of the low risk of regulatory agency involvement, to assure the quality and safety of the material being produced. If the regulations and guidance are examined, it becomes apparent that there really is a regulatory requirement that drives the application of Good Manufacturing Practices to all phases of clinical material manufacturing intended for human or animal use. Where is this requirement actually written down? In the European community, Annex 13 applies specifically to the manufacture of investigational drug product. It carries similar language to the Q7A document. The Commission Directive 2003/94/EC must be placed into law this year. It also contains specific language that includes investigational drug products under the umbrella of GMP. The GMP regulations and guidance are actually very similar for both FDA and the EU (European Union). FDA audits usually begin at the GCP (Good Clinical Practices) stage, then only for GMP when application for registration has been made. The FDA will not generally inspect a facility for clinical phase manufacturing unless they have cause, possibly because of an adverse event associated with the clinical testing of the material. They could also review some of the data generated to support a license application when the pre-approval audit for registration is performed.

The actual application of GMP for the manufacture of material at the investigational

stage is not specifically found in 21 CFR 211. Nor is it specifically found in the various FDA guidance. Its relevance is actually found in the Preamble to the GMPs. Written in 1978, the Preamble is the commissioner's answer to the many questions and comments preceding the final approval of the Good Manufacturing Practices. It clarifies the intent and scope of 21 CFR 211. It states "these GMP regulations apply to the preparation of any drug product for administration to humans, including those still in investigational stages." There are two items of significance: GMP applies to clinical trial material, and the implication that GMP applies not only to Phase 3 material, but also Phase 1 and Phase 2. It goes on to say that the process by which a drug product is manufactured in the development phase be well documented and controlled in order to assure the reproducibility of the product for further testing and ultimately for commercial production.

There is a clear requirement to apply GMP to the manufacture of investigational drugs. The European Directives state it clearly in their principles. The FDA buries it in the preamble to the GMPs. The language in all these documents puts the safety of the trial participants at the forefront. Companies must exercise due diligence, regardless of the low risk of regulatory agency involvement, to assure the quality and safety of the material being produced. These Regulations and Directives, in effect, answer the question of whether GMPs are applied. The next question to answer is how are they applied? To answer this, we must start examining the guidance.

## The requirement for GMPs during Clinical Trials

Several FDA Guidance Documents help to interpret the application of the regulations. The International Conference for Harmonization approved Q7A, the Good Manufacturing Guide for Active Pharmaceutical Ingredients in August 2001. This guidance is almost repeated verbatim in the European annexes. While it does

**Q7A: Table 1**

Type of Manufacturing	Application of this guidance to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of API starting material	Introduction of the API starting material into process	Production of intermediates	Isolation and purification	Physical processing and packaging
Biotechnology-fermentation- cell culture	Establishment of Master Cell Bank and Working Cell Bank	Maintenance of Working Cell Bank	Cell Culture and /or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" fermentation to produce an API	Establishment of cell bank	Maintenance of cell bank	Introduction of cells into fermentation	Isolation and purification	Physical processing and packaging

not address the manufacture of bulk or finished drug product, it applies specifically to the preparation of Active Pharmaceutical Ingredients, which are the pre-cursor to the bulk or finished drug product.

This guidance includes two specific sections that address clinical trial materials.

- First, there is a matrix table at the beginning of the guidance that indicates where in the process GMPs apply. An excerpt is shown here. Table 1 addresses the various manufacturing processes such as chemical manufacturing, and the fermentation processes. While the shaded boxes in this table clearly indicate the boundaries, it has been expected that elements of GMP are applied to stages even earlier than those indicated. In the fermentation technologies, GMP doesn't officially start until the working cell bank stage, or even until cells are actually introduced to the fermentor. It would be a bit fool hardy to think that no quality elements should be applied to the previous steps such as establishment of the master cell bank or, for the classical technology, the maintenance of the cell bank. European and US inspectors usually request these documents for review.
- Q7A also contains a section dedicated solely to the Clinical Trial materials. Part 19 is entitled APIs for Use in Clinical Trials. Here is where the "guidance" for application to investigational medicinal products is found. The "controls should be consistent with the stage of development" and Process and "test procedures should be flexible" to provide for change. This is where the rest of the discussion will focus.

Even at the clinical trial/investigational drug stage, companies should assure themselves that the actual performance or lack thereof attributed to their potential blockbuster drug is not skewed or biased by poor handling, storage, manufacturing problems and so on. Good Manufacturing Practices help assure that the performance is not affected by poor control and that safety is not compromised because of poor practices. The European GMPs state that they do not want to confuse lack of efficacy due to lack of drug capability with lack of efficacy due to poor quality practices.

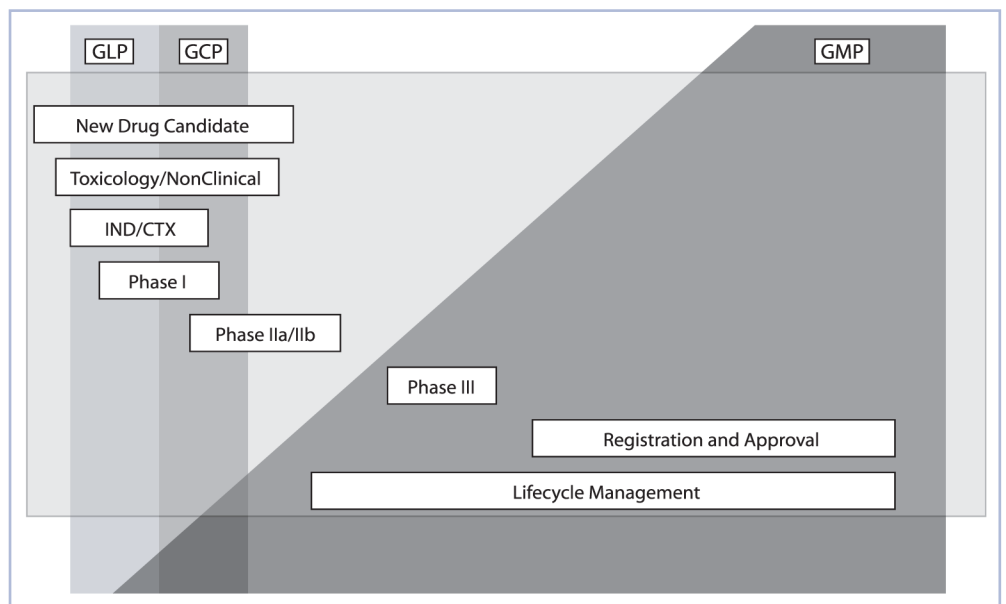
Some common themes can be derived from all this. It is important to have a well

documented development and manufacturing process, maintained under change control. The intent is to develop a reproducible process that provides reliable results that can be used to defend a process. The manufacturer must understand their process. This cannot be achieved if the above elements are not assured. Even during Clinical Trial development, certain elements of quality must be built into a process at the beginning and not tested into it at the end. Application of principles of GMP help to assure that this control, reproducibility, and reliability are built in throughout the process.

## How should GMPs be applied to manufacturing during Clinical Trials?

The regulations tell us that we must apply GMP. How we apply GMP is the key, flexible to the stage of development. Once it is established that GMPs must be applied, the next challenge is to figure out how to apply them. At small, under resourced facilities, without the benefit of a mature Quality System umbrella to support their efforts or an established manufacturing organization to work within, a calculated, risk based approach to the application of the principles of GMP can be developed. This is practical approach to applying GMP to early stage manufacturing for investigational medicinal products intended for human use.

The approach to implementation is based upon an individual risk assessment that evaluates the stage of development, resources available, type of product, intended market and other relevant criteria. Before quality systems can be applied, they need to be identified and an implementation plan developed. As Q7A states, the



flexibility is found in the stage of development. With this statement as the basis for the strategy, Quality System matrices can be developed as guidelines to the implementation of Good Manufacturing Practices appropriate to the stage of development.

The application of quality practices can be viewed within a product development diagram. Once small quantities of a drug candidate are available, it may undergo toxicology and non-clinical trials. Following success in these preliminary studies, an IND (Initial New Drug) application may be submitted so that human trials may begin. Trials progress from Phase 1, for safety and dosing, to Phase 2 and 3 for efficacy and determination of indications. Following successful trials, the candidate drug can be licensed for commercial manufacture.

Good Laboratory Practices are applied at the non-clinical stage. Good Clinical Practices apply to the execution of the clinical trials. The manufacturing, testing, and release of the materials used for these human clinical trials must be performed with some conformance to Good Manufacturing Practices. As illustrated in the diagram, it can be seen that GMP is relevant at all phases of development, with increasing robustness and rigor as the material nears the goal of registration and market approval.

The Quality Systems are applied on a continuum. From the beginning, even in development, elements of GMP must be applied. The closer to registration, the more rigorous the application of GMP. Examples of relevant quality systems include Documentation Program, Calibration Program, Training Program, Validation Policy, Maintenance Program, and Change Control program. The list gets more involved as the product progresses through development.

## Implementation of a GMP Matrix

Start by listing all the Quality Elements or Quality Systems that are applicable and then place them into a matrix representing the various phases of product development. Most elements are relevant and applicable for all phases. In these cases, where the Quality System is identified as a requirement for each phase, a secondary matrix is developed that identifies discreet elements within the quality system. This secondary matrix defines the flexibility within the system.

The degree of application and the level of requirements increase as the phase of development progresses. These matrices will provide continuity and consistency from project to project and also between functional groups such as Development and QC. The degree of application and the level of requirements increase as the phase of development progresses. Some examples show the

progressive implementation of GMP elements for several Quality Systems pertinent to all stages of development.

- One example of an important Quality System program is for Raw Material Management. All materials are received with a certificate of analysis, but an actual specification is not required until Phase 1. This goes towards the earlier Phase 1 Guidance recommendation that control begins with the Raw Materials. Once an approved specification is issued, the contents are now under change control -- control being another early requirement from the Guidance Documents. Testing requirements increase as the Phase of development progresses. Phase 2 may include only ID testing and Phase 3 would add full analytical analysis of each material. This approach provides a flexible Quality Assurance program for raw materials to match the requirements of each phase. It also helps small firms with limited budgets and staffing to develop manageable, yet defensible programs for their early phase materials.
- A second example relates to utilities and facility. While it may not be practical to fully validate systems in the early phase manufacturing areas, it is still important to have an adequate monitoring program that assures the quality of the materials being used. The degree of validation progresses from IQ to OQ to PQ with the phase of development. And all systems, once qualified to any degree, are maintained under change control. These GMP matrices are then used as the foundation for a Facility Certification process. A strategy to "certify" the facility can be developed. This certification strategy provides a pre-defined level of GMP that represents a position of acceptable risk for manufacturing at a particular phase. It is important to provide consistency within the Quality Systems that have been developed, even if flexibility in application is expected for each phase. The flexibility within the system is defined within the quality system matrices and then translated into the certification strategy.

"Certification" provides a visible, formal program that all employees can see, understand, and participate in. Product safety and quality are often demonstrated after the fact, using the electronic system or paper product as the final proof. That is exactly what the GMP Certification process is meant to achieve. The final result is a Documentation Package that demonstrates Manufacturing and Quality System readiness appropriate to the stage of development.

The certification is partly accomplished through an assessment of requirements matrices. These assessments are translated into summary tables, status reports, and action plans. The Certification effort addresses all the quality systems. Part 11, Cleaning Validation, and other relevant systems or quality elements could be included specifically or indirectly in the assessments. The scope of work is translated into a checklist for the relevant quality systems. If the Quality Element is not implemented at this

point, the checklist identifies it as a gap in the Readiness Assessment.

The detailed evaluations, scientific assessments, and so on are managed at the lower levels. Using the Procedures and Policy, the anticipated stage of development is addressed. From the matrices the expected level of application is selected. From there, a checklist of procedures, protocols, and other relevant documentation, such as change controls, deviations, or internal audits are developed. This checklist becomes the action plan against which the readiness status is measured. Once the checklist is executed, a gap analysis is performed and a remediation plan is developed. The basic checklists are incorporated into the Certification Procedure. These are the elements expected to be in place.

A separate checklist can be developed for each phase so that individual assessments can be performed as necessary. Remember, according to the matrices, Phase 2 may have additional requirements or require a more rigorous application than the Phase 1. The certifications can be executed in sequence. In this manner, once certified for Phase 1, the firm can build upon that for Phase 2 certification. This allows the firm to approach full GMP conformance in stages that are appropriate to the level of financial and human resources available to them. In addition to the checklist, a certification procedure should include a requirement to document the status of facility, utilities, and manufacturing and laboratory equipment.

These assessments include a list of the equipment, operating procedures, maintenance and calibration programs, and validation protocols. Once the assessments are complete and a gap analysis is performed, outstanding deviations, such as problems with utilities or microbial issues should be resolved. Findings from GMP audits should be addressed. Finally, a determination is

made based on the findings that Clinical Trial material for human use can be manufactured to an acceptable standard of quality, safety, and reliability.

A corrective action plan with milestones should be developed. This plan is used to track progress on continued improvement in the conformance to GMP expectations for the relevant phase of manufacture. Once all the assessments and corrective actions and milestone plans are completed, a Certificate of Conformance can be devised for symbolic display. This provides management, development, and operations personnel with a sign that the facility is in a state of GMP readiness as well as Manufacturing Readiness. It also provides outsiders, such as auditors or clients, with a visible sign that a process for assuring that GMP is important and that it is an active part of the manufacturing and quality systems.

As a firm progresses from Phase 1 to Phase 3, the process is repeated and GMP Certificates are issued as each level of conformance is attained. Once a level of Certified Status is established, the next challenge

is assuring that the quality systems are maintained. For development facilities striving to become GMP manufacturing facilities, it is easy for the personnel to slip back to the "old" ways of doing things. It is important that they stay accountable to the implemented systems. GMP is not a switch that is selectively applied on a day to day basis. Gowning practices, material movement, raw material receipt, document management, etc. all have to be maintained and applied consistently. The first level of certification is used as the building block for the second and third level of certification.

In conclusion, there are many elements of GMP that must be in place before manufacturing can begin. It is important that appropriate quality systems and strong documentation, audit and traceability packages are in place to support them. Reliable electronic systems or paper audit trails are the secondary product that last far longer than the actual medicinal product. The electronic systems or paper products provide the proof that quality elements and GMP principles were applied during the process. They must also be factored into project timelines to ensure GMP compliance without inhibiting timelines or breaking budgets. Procedures must be written, equipment qualified, personnel trained, batch records developed, changes evaluated. All these are important, necessary, and often overlooked as project teams strive to get the product to the clinic as soon as possible. GMP can be implemented without a massive commitment in resources. GMP can be used to streamline the transition from clinical trials to commercial manufacturing.

## Research References

1. 21 CFR-Preamble to the GMPs, 1978 Final Rule
2. Guidance for Industry- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-characterized, Therapeutic, Biotechnology-derived Products; November 1995
3. Guidance for Industry- INDs for Phase 2 and Phase 3 Studies; Chemistry, Manufacturing and Controls Information
4. Annex 13: Manufacture of Investigational Medicinal Products, Revision 1, July 2003; Volume 4 Good Manufacturing Practices
5. Q7A: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
6. Kuwahara, S.S."Good Laboratory Practice to Good Manufacturing Practice Transitions During the Product Development Process"; Journal of GXP Compliance, October 2002
7. 21 CFR 312 Investigational New Drug Application
8. Draft Guidance for Industry: Analytical Procedures and Methods Validation; Chemistry, Manufacturing and Controls Documentation, August 2000



**USA: Global Headquarters**

CDC Software  
Two Concourse Parkway  
Suite 800  
Atlanta, GA 30328  
USA

t: +1 770.351.9600  
f: +1 770.351.0036

**United Kingdom**

CDC Software  
Pioneer House  
7 Rushmills  
Northampton NN4 7YB United  
Kingdom

t: +44 1 604 630050  
f: +44 1 604 630495

**Spain**

CDC Software  
Frederic Mompou 5  
Ed Euro 3  
08960 Sant Just  
Barcelona  
Spain

t: +34 93 480 28 50  
f: +37 93 480 28 55

**Netherlands**

CDC Software  
Sparrenheuvel 32, 3708 JE Zeist  
Postbus 967, 3700 AZ Zeist  
Netherlands

t: +31 30 288 8454  
f: +31 30 288 5238

**For more information or a complete list of our worldwide offices, please visit [www.rossinc.com](http://www.rossinc.com).**

Copyright © CDC Software 2008. All rights reserved.

The CDC Software logo and Ross Enterprise logo are registered trademarks and/or trademarks of CDC Software.