A Risk-Based Approach to cGMPs

?? Scope

?? Goals

?? Definition

?? Introduction

?? Background information

?? Guiding principles to achieve these goals

?? Controls to achieve goals

?? Conclusion

?? Addendum
- Examples of using risk-based management principles
- Existing requirements

Committee Members:
Chair, D. Bruce Burlington, Wyeth
Dave Haggard, Merck
Ed Kaminski, Wyeth
Frances Sakers, Wyeth
John Grazal, Astra Zeneca
Janice Whitaker, GSK
Erika King, PhRMA

10/16/02

Executive Summary

FDA is undertaking an initiative to use a science-based risk management and integrated quality systems approach to pharmaceutical cGMPs. This document is a PhRMA position paper describing the principles for this new approach to cGMP regulation. A new approach to current GMPs designed using the science-based risk management approach will establish a system that serves patients by ensuring product quality, supports product availablility, encourages technological and innovative advances, removes subjectivity that currently exists in some areas, and reconciles FDA's decisions with the decisions manufacturers must make about products rather than relating cGMP to an abstract set of requirements.

A collaborative and unified effort (including FDA, industry and scientific experts) is needed to establish: revised regulations and compliance policy guides, inspection approaches and plans, and an enforcement program for cGMPs and the CMC section of an NDA submission. Focus must be on the principles underlying science-based cGMPs to offer benefit to regulators, industry and ultimately patients.

The major goal of the cGMPs and CMC on drug manufacturing and testing is to provide patients with a product that has an equivalent identity, safety, strength, quality and purity to the one used to establish the clinical database. The basis for making "risk-based" decisions is the risk to patients. GMP regulations based on the principle of risk-based decisions would include requirements for product based health hazard analysis of critical control points in the manufacturing process. Risk-based GMPs would then focus on control of critical control points necessary to ensure that the finished product meets the quality attributes required for the patient use. Greater flexibility in how the critical points are controlled would serve the public and industry well. Without this flexibility, industry is dependent on regulatory discretion in the manner in which prescriptive GMP regulations are enforced.

Risk-based GMP regulations would not adversely affect the quality of drug products but rather focus attention and controls on the critical manufacturing points and the attributes that define quality to the patient. Integrated with the Quality

Systems Approach, this method is the most efficient and effective means of establishing a new approach to cGMPs that will sustain patients, regulators and industry in the future. Today, the American health care system needs a concept of cGMPs that reflects and embraces modern scientific and technological realities and, at the same time, places drug product fitness for use as the ultimate goal.

Scope

This document proposes a framework and describes principles for a science-based risk management system for cGMP regulation. Specific recommendations regarding risk models and categories of risk are not included. The cGMP system encompasses the quality policy, manufacturing controls, application review, inspection, and enforcement processes. In considering such a system, factors such as availability of product, use of products by patients, GMP compliance record of firms, inherent risks of various drugs or formulations, and analysis of product characteristics and technologies must be considered.

Goals

The major goal of current Good Manufacturing Practices (cGMPs) and the Chemistry and Manufacturing Controls (CMC) on drug manufacturing and testing is to provide the patient with a product that has as good as or better identity, safety, strength, quality and purity to the one used to establish the clinical database.

Additional goals are to provide a framework for manufacturers' quality policy, product availability, and FDA's inspection and enforcement activities.

Definition

Science based risk management as applied to the cGMPs focuses on the patient's perspective. The patient expects a product to be fit for use and to be available when the patient wants to use it. The attributes of being safe and efficacious, having the expected appearance and convenience, being readily identifiable and free from extraneous material are key elements of being fit for use.

Quality is fitness for use.

Introduction

In order to meet patients' expectations the formulation and implementation of risk-based cGMP should include the participation and collaboration of the following organizations:

1. FDA
    - ?? Review Centers (reviewing chemists and compliance staff)
    - ?? Office of Regulatory Affairs and District Offices (field investigators and enforcement program)
2. Pharmaceutical companies
    - ?? Manufacturing
    - ?? Pharmaceutical development
    - ?? QA/QC
3. Expert Scientific Community

FDA's plan to use a science based risk management and integrated quality systems approach to pharmaceutical cGMPs is both a needed and welcome initiative from the PhRMA perspective. Any revision to the cGMP regulations and/or adoption of an industry practice as a cGMP should be in this context.

An emphasis on the principles underlying science-based cGMPs will provide a solid platform for the revised cGMP regulations and adopted practices. They will also assist in an equitable interpretation by both industry and FDA investigators. The same criteria, of science-based risk management and integrated quality systems, should be applied to the requirements for the CMC section of an NDA submission. Such a unified approach to the cGMPs and the CMC section of the submission, in terms of requirements, review and interpretation; will benefit both regulators and industry.

Background Information

FDA establishes the cGMPs through regulations, and guidances, which adopt those industry control practices that are applicable and feasible to drug production generally and permit specific interpretations for a particular company or product. The cGMPs are intended to be valuable by contributing to the assurance of drug identity, safety, strength, quality, and purity.

Manufacturers must establish and maintain quality systems to assure that drug products are manufactured, held, and distributed in accordance with the cGMPs and with the product application or license commitments. And the FDA inspects facilities to confirm manufacturers compliance to cGMPs.

In addition to generally applicable cGMP, the FDA approves the product specific Chemistry and Manufacturing Control requirements that a manufacturer must adhere to in order to assure the identity, strength, quality, and purity of the product.

Chemistry and Manufacturing Controls, Quality Assurance/Quality Control programs and current Good Manufacturing Practice requirements are designed:

- First, to assure the equivalence of the commercial drug product used by patients, as it relates to the identity, safety, strength, quality and purity (but not trade dress or dosage form) to that used in the clinical trials database. This is needed to establish, from the drug product perspective, the ability to predict the response of new patients.

  - The strength of the drug substance in the dosage form needs to be the same as that studied (or related to the study in a precise way). This parameter is measured as a concentration - weight/weight, weight/volume, unit dose/volume, etc. and /or as the potency as indicated by appropriate laboratory tests such as weight and content uniformity and for the stability requirement.

  - The drug product bioavailability must relate to that used in the clinical trials in a systematic way. This leads to the requirements for dissolution and contributes to the requirements for stability.

- ✍ Foreign substances, cross-contaminants and any other extraneous materials in the drug product that might adversely impact the health of the patient must be prevented through adequate control of the components as well as the adequate maintenance and calibration of equipment in the factory.

- ✍ Microbial agents need to be controlled to the extent they could cause product deterioration or adversely affect the health of patients. To evaluate the health risk associated with microbial agents, the dosage form, the target patient population, the type and estimated number of microbes, and the ability of the microbe to survive the processing steps should be considered. For example, an opportunistic pathogen would pose a health risk to an immuno-compromised patient, whereas it would pose negligible risk to a normal patient. Low levels of microbes, excluding enteropathogens on oral dosage forms would not pose a problem.

?? Second, the manufacturing process must be characterized, monitored and controlled to assure that batches consistently meet their pre-determined quality attributes.

?? Third, the documentation associated with the entirety of the manufacturing process must be sufficiently detailed to demonstrate that the manufacturing process was adequately controlled. But documentation in and of itself does not establish quality and the patient is not well served by obsessing on documentation. Minor disparities in documentation do not in and of themselves indicate a given lot of product, otherwise conforming to all specifications, is not fit for use. The documentation also serves to identify any trends to provide for traceability useful in any investigations, and efforts to improve the manufacturing process and controls.

<u>Guiding Principles to Achieve These Goals</u>

?? The systems of controls within manufacturing (documentation, validation, change controls, training, laboratory controls, etc.) are valuable to the extent they ensure or improve the manufacturing process and are necessary to ensure patient safety.

?? Conversely, controls that do not advance the above goals are not risk-based and are impediments to the availability of drug products. Approaches to cGMP can serve patients poorly if they ignore the fundamental fact

that patients expect marketed products to be fit for use. Whether or not to have a product on the market is a binary decision. Any controls, inspection plan, or enforcement program that does not recognize this is not patient oriented. Such controls represent a diversion of effort away from assurance of adequate drug product quality, drug availability, and impact the resolution of problems that might legitimately affect patients.

?? The FDA and industry work in a collaborative manner to address drug availability (potential & real shortage) matters. In assessing the underlying cause of availability if production issues are identified through inspection, the measure of significance should incorporate a risk-based philosophy with special weight given to the medical need and benefit of the product availability to the patient.

?? Technological advances in processing and testing, when established through scientifically designed programs, should be encouraged. Implementation of risk management principles should guide both the industry, in its implementation, and the Agency in establishing requirements for notification, documentation, review and inspection of these advances.

?? Regulatory scrutiny of changes should be risk based, in line with risk management principles, and the use of alternative criteria to prior approval review, such as comparability protocols, should be expanded.

?? Inspection plans, duration, and intensity of scrutiny must take into account the inherent risks of products as well as the past compliance status of the site.

Controls to Achieve Goals

The administration of the existing systems of submission requirements, manufacturing controls, and inspections as well as the enforcement approach related to these systems requires reevaluation.

?? Critical-to-quality parameters and critical control points require special consideration (as opposed to non-critical parameters) that are also included as part of the NDA package. For example, deviations from non-critical parameters (i.e. those established to optimize a process or based on process capability) should not require the extensive cGMP documentation mandated by 21 CFR Sec 211.100. Changes in non-critical parameters should not require extensive validation or sNDA submission.

?? A key aspect of a well-controlled commercial process is successful technology transfer. This link between the pivotal clinical batches and the proposed commercial process should in major part serve to satisfy the parameter of fitness for use for the commercial product.

?? The integration of new technologies, such as Process Analytical Technology (PAT) and other in/on/at line controls will lead to increased levels of process and product knowledge and quality assurance. These technologies and other related advances should prompt a shift in the concept of process validation. In effect, the application of some of these new technologies renders every batch a "validation batch". Where one can use PAT to establish process capability there is no need to validate the potential process excursion range; one has only to maintain the process within demonstrated capability. Even before revision of the cGMPs the FDA "safe harbor" concept should be extended to encourage industry efforts to adopt new controls.

?? New technologies have also greatly increased the level of control and monitoring available for facilities, equipment, utilities, etc. These enhancements should also be viewed in the context of risk-based cGMP requirements.

Conclusions

A science-based risk management model integrated with a Quality Systems Approach is the most efficient and effective means of establishing cGMPs that will serve patients, the regulators and the industry well into the future. A collaborative effort between the FDA, the industry and scientific experts is the best means of achieving the paradigm shift that will benefit all concerned parties. Starting with the cGMP regulations and extending through requirements for the CMC section of NDA submissions, the goal should be to evaluate requirements from a science based, patient oriented risk perspective. Designing the cGMPs using such an approach will establish a system that can withstand rigorous scrutiny while, at the same time, removing the subjectivity and pseudo-science that currently exists in some areas. Disputes in interpretation of cGMP should be resolved on the basis of good science and objective risk-based principles under rules that are well understood, visible across the regulated industry and the Agency, and rigorously enforced by both industry management and the FDA.

Risk-based cGMP regulations do not reduce the quality of drug products but rather focus attention and controls on the critical manufacturing points and the attributes that define quality to the patient. Risk-based cGMPs encourage technological

advances that can improve the manufacturing process because it frees the manufacturer from prescriptive regulations that do not improve quality. An added benefit is that risk-based GMP regulations may reduce costs not related to quality attributes.

The combination of reduced resources, both human and financial, increased complexity in all aspects of drug manufacturing, and the availability and continuing emergence of new technologies all point to an urgency in changing the way the industry and the regulators perform their respective functions. The cGMPs have served us well over the years but the world of pharmaceutical manufacturing has changed drastically in the years since the last major revision of the cGMP regulations. What is needed today is a system of cGMPs that reflects and embraces modern scientific and technological reality and, at the same time, places drug product fitness for use as the ultimate goal.

Addendum

?? Examples of using risk-based management principles

- ✍✍cGMP documentation requirements should be reviewed with a goal of reducing unnecessary detail, and promoting the use of electronic means of capturing data. The criteria for this review is fitness for use (quality).
- ✍✍If the product has been on the market for years and new technology allows greater product evaluation/scrutiny, it should not be necessary to provide such (e.g., enhanced impurity detection) if the product is actually fit for use.
- ✍✍A science based risk management approach should not only impact the cGMP regulations; these concepts should permeate the entire manufacturing process all the way down to the shop and laboratory floor.
- ✍✍Development of a risk management approach to cGMPs should provide a framework for decisions concerning frequency, depth, and scope of regulatory inspections.
- ✍✍The process of developing a risk management approach to the cGMPs should include, in its scope, much greater clarity regarding when regulatory actions should be taken.
- ✍✍Stability testing programs should aim at avoiding toxic degradants and assuring that variations in content at the point of use will be small relative to the variation in the achieved in vivo drug levels. The amount of acceptable variation in drug content should be evaluated in the context of the breadth of the therapeutic index for the product.

?? Existing requirements

The structure of the existing requirements and how they relate to assumptions about batch control and validation, with (statistical) sampling and testing should be explored from a level of risk perspective on the shop floor and in the laboratories:

- ✍✍Process Definition – Process definition can be enhanced by application of tools such as statistically-based experimental design, critical control point analysis, and other techniques to provide a firm foundation for

establishing product specifications. The use of a risk-based approach in determining product critical specifications vs. less critical monitoring and process capability levels is an area where significant progress can be made.

- Deviation and Error Investigations – Problem solving tools and models that have been effectively used in many other industries (such as the auto manufacturing industry) to determine root/actual cause should be encouraged in a risk-based approach to cGMP. A quality system for investigations should be designed and implemented which involves management notification, timeliness, and trending of corrective and preventive actions. The goal of such a system is to prevent recurrence of manufacturing errors.

- Problem Resolution – A firm can have a process for investigations of manufacturing discrepancies and perform work against that process. However a program of integrated management notification, timeliness, and thorough root cause analysis in applying the requirement represents a lower risk. (This might also include reporting requirements to FDA).

- Testing, Measurement, and Parametric Release – A manufacturing process that exploits advances in technology to increase the monitoring and assurance of critical parameters during batch production activities a more robust process than one which relies on sampling and off-line testing. Provision should be made to encourage a regulatory and cGMP system that encourages these advances and recognized their superiority over traditional methods.

- Management Controls – (e.g. organization, quality plan, communications, involvement, knowledge, etc)- The sum total of the management controls brought to bear on the manufacture of quality products must be recognized in a risk-based cGMP environment. The industry should actively seek to, and have the regulatory freedom to design the most effective systems for the products being manufactured.

- Training – Training programs in the industry and the Agency should be enhanced to meet the future challenges of greater technology and a changing cGMP environment. The essential element of training must be given higher priority. A firm whose training program follows the apprentice through journeyman and then master operator concept, for example, may represent a lower risk base.

- Document Control – The balance between detail, understanding, usability, and value of written procedures and other documents should be struck in the context of a new risk-based cGMP environment.

- Validation – Validation is an area that exploded from its original concept relating three controllable variables in steam sterilization processes (time, temperature, and pressure). The assurance of a consistent process that meets its pre-determined quality attributes should remain the standard in the new risk-based cGMPs. The challenge should be to determine if advanced monitoring and control of support and other systems has supplanted the value of validation in assuring product quality.

- Change Control – The awareness and assessment of changes in a controlled system is a proven control concept. The level and type of change that must be officially reported to the Agency should be permitted to evolve in the risk-based cGMP environment. Changes that would have improved process controls or drug product consistency have been delayed or even abandoned due to current reporting requirements.