This paper proposes an organized approach to compliance—compliance by design (CbD) documented in a compliance master plan (CMP)—based on approaches used in quality by design (QbD) and the validation master plan (VMP).

QbD has transformed new product development and pharmaceutical manufacturing by means of a logical and systematic approach. The VMP is a well accepted set of documents that contains validation information and commitments for the organization. The methods of QbD and VMP may be similarly applied to pharmaceutical compliance in CbD and CMP with correspondingly successful results.

CbD addresses compliance as a target objective—the “products” of the quality systems. The approach is analogous to the QbD approach to pharmaceutical product development, pharmaceutical products, and continuous improvements. The proposed CbD approach specifies compliance objectives and attributes, identifies critical compliance parameters, defines input variation and a control strategy, and manages compliance improvement commitments. The CbD approach is organized according to the US Food and Drug Administration’s quality systems structure.

The CbD effort may be documented through a CMP analogous to a VMP. In addition to basic systems descriptive information, the CMP would contain commitments and timelines for correction of deficiencies and compliance improvements as done with validation commitments in the VMP. Risk analysis and process analytical technology (PAT) are part of CbD/CMP. The CbD/CMP approach provides an organized focus on compliance, enhances cross-functional thinking, defines the commitment and improves transparency of the organization’s compliance effort, clearly identifies accountability, facilitates audit preparedness and performance, and provides a standardized audit documentation format.

An organization embracing the CbD/CMP approach demonstrates a strong commitment to compliance. Documenting the CbD approach in a CMP requires transparency in the compliance effort. An organizational commitment including transparency should positively impact the organization’s credibility of the compliance effort with auditors and with employees responsible for performing the work of compliance.

INTRODUCTION
The US pharmaceutical industry has experienced great advancements in development and control of manufacturing processes. The QbD effort (1) has transformed new product development in only a few years. The scientific community has responded through professional association collaborations and as individuals in publishing conceptual approaches, methods, and research. This effort has resulted in new and more sophisticated development and manufacturing approaches (2, 3, 4). Further, it has facilitated implementation of modern technology that is now commonplace in the pharmaceutical manufacturing environment.

While now celebrating QbD technical process advancements, the industry has simultaneously experienced several terrible and well publicized events. People have died from occurrences connected to
pharmaceutical products. These events have not been caused by manufacturing process problems, but rather are associated with deficiencies in compliance. All these problems do not have the same root cause. Some were caused by deliberate criminal actions (e.g., heparin deliberate substitution by oversulfated chondroitin sulfate [China] and diethylene glycol deliberate substitution for propylene glycol [various countries]). Other problems, however, were preventable, (e.g., Vi-racept cleaning [Switzerland] and Methotrexate/Cytarabine contamination [China]. Other business factors (e.g., LEAN minimizing excesses [5], inexperienced workforce, reduced headcount, increased workload) may have contributed to these problems.

Drug manufacturing regulations are based in the FDA good manufacturing practices (GMP), conceptualized in 1941 and formally introduced in the 1970s (6). These regulations have been significantly enhanced through a management systems approach (7, 8, 9). The application of risk analysis to quality systems was also recently introduced (10, 11, 12). These changes have improved the approach to GMP compliance, making compliance more comprehensive, integrated, and focused on areas of the greatest impact.

Can anything more be done to further improve compliance, either in performance or efficiency? Specifically, can compliance programs apply methods or approaches successfully used in the QbD initiative and in validation? Might these approaches help to address potential compliance problems proactively, rather than only responding to actual problems after they occur? Can the compliance effort be better organized to enhance and optimize performance?

APPROACHES AND METHODS TO IMPROVE COMPLIANCE

This paper proposes an organized approach to compliance (i.e., compliance by design and a compliance master plan) based on successful industry experiences with quality by design and validation master plans.

The recent successes of QbD and associated initiatives have prompted an evaluation of QbD methods for possible application to compliance. The process analytical technology (PAT) and quality risk management guidance are also relevant in this review. Concepts in process validation and the VMP are widely used and may be similarly applied to compliance. The following briefly discusses well-accepted pharmaceutical methods and approaches that have evolved within pharma and the regulatory environment. Certain aspects of these approaches may be successfully applied to compliance.

Quality by Design

The QbD concept became widely known during the 2000s and has evolved to emphasize and clarify the most important elements of new product development. Various methods in QbD (e.g., design of experiments, design space) have been used for many years. The QbD effort has successfully organized, structured, and focused these methods and applied them throughout the entire product lifecycle.

The basic information determined during development forms the technical basis for ongoing commercial manufacturing. The following key aspects of QbD have been recently identified (13):

- **The quality target product profile (QTPP) and critical quality attributes (CQAs).** These are the fundamental requirements for the product to be developed. A product development effort requires a clear definition of the dosage form to be developed and the critical attributes expected for the product.
- **Drug substance and excipient properties.** This topic comprises the thorough characterization of the active pharmaceutical ingredient (API) and key excipients including compatibility studies.
- **Formulation design and development.** This addresses the laboratory scale development of the formulation and other non-clinical formulation development studies.
- **Manufacturing process design and development.** This addresses development of the manufacturing process, including facility, equipment, material transfer, and manufacturing variables.
- **Identification of critical process parameters (CPPs) and critical material attributes (CMAs).** This addresses the relationships between materials, processes, and the critical quality attributes of the dosage form.
• **Risk assessment and design space.** All development activities should be conducted with risk in mind to determine which studies to conduct, where knowledge gaps exist, and to help develop appropriate control strategies.

• **Scale-up and control strategy.** These are final steps in development involving commercial scale processing and methods to minimize variation due to materials and processes, real time testing, product specifications, and ongoing process monitoring.

The product and manufacturing process is continually monitored and updated to assure consistent quality during the product commercial lifecycle. Continuing improvements in product and process are expected with ongoing manufacturing experience. International Conference on Harmonisation (ICH) Q8 (14) is consistent with this discussion.

### Process Analytical Technology

The final FDA PAT guidance (15) was issued in 2004. This guidance encourages holistic implementation of new technology in pharmaceutical development, manufacturing, and quality assurance. In general, this guidance espouses building quality into products and processes rather than testing quality into products. PAT is a component of the QbD strategy because it helps with process understanding, process control, and minimizing output variation. Topics addressed in the PAT guidance with particular applicability to compliance include PAT tools such as process analyzers and process control tools. Evaluation and implementation according to risk is encouraged. New technology should be considered to facilitate improved compliance and to build quality into compliance systems whenever possible.

### Risk Analysis

All activities in pharmaceutical development, manufacturing, and quality assurance should be conducted with consideration for risk to the patient. FDA and ICH documents (10, 11, 12) clearly state this position.

### Quality Systems And GMPs

FDA first issued the quality systems approach to current good manufacturing practice (CGMP) (16) in the early 2000s. The quality systems approach complements CGMP by emphasizing a quality system infrastructure supportive to the compliance effort. Specifically, it addresses management responsibilities to provide resources to perform and maintain compliance activities. Further, it organizes the individual components of the GMPs as categorized in 21 CFR Part 211 into the following functional systems for purposes of regulatory audits:

• **Quality system.** The quality system assures overall compliance with CGMPs and internal requirements. It includes the quality unit and its responsibilities in batch release, annual product reviews, product defects, validation, and similar functions.

• **Facilities and equipment.** The facilities and equipment component addresses measures and activities that provide the physical environment used in the manufacturing of drug products. It includes buildings, facilities, equipment, HVAC, water systems, other utilities, and associated validation and qualification.

• **Materials system.** The materials system addresses activities to control finished products, components, closures, and water. It includes material inventory systems, validation of these systems, drug storage, distribution controls, and associated records.

• **Production system.** The production system includes measures and activities to control the manufacture of API and drug products including batch manufacturing, in-process sampling and testing, process validation, and associated documentation.

• **Packaging and labeling.** The packaging and labeling component addresses measures and activities that control the packaging and labeling functions including label examination and usage, label storage and control, packaging and labeling operations controls, and associated validation.

• **Laboratory control system.** The laboratory control system addresses measures and activities related to laboratory procedures, testing,
method development and validation, and stability programs.

**Process Validation**
The lifecycle approach to process validation was presented to the industry during the mid 2000s. The draft guidance document discussing this concept was issued in November 2008 (17). The lifecycle approach clearly expands process validation to include product design and development, as well as the ongoing monitoring of product and process performance throughout product commercialization. The “three-lot definition” of validation has been relegated to that of a brief snapshot in the product timeline. The three stages of the lifecycle approach to process validation include process design, performance qualification, and continuous process verification. The approach described in the process validation guidance is consistent with QbD.

**Validation Master Plan**
The validation master plan is a well-accepted document in pharmaceutical manufacturing (18, 19, 20, 21). In brief, it describes the respective manufacturing and support systems in the manufacturing facility and the validation and qualification plans for the same. Sections describe equipment, facilities, utilities, and other systems and lists individual components. Listing of validation and qualification documentation for these systems is provided. Product process validation, cleaning validation, and analytical methods are also listed with applicable validation documentation. The VMP also contains a schedule of validation work to be accomplished in the next year or subsequent years. This work may include new equipment to be installed, corrective action, planned changes and validation, revalidations, and so on. The VMP thus provides reference for validation documentation supporting current systems, as well as a commitment for planned future validation work. All validation and qualifications are listed in the VMP across all quality systems. The VMP is almost always requested to be reviewed in regulatory audits and is often one of the first documents to be requested.

**QUALITY BY DESIGN AND COMPLIANCE BY DESIGN**
This paper proposes the application of QbD strategies and approaches to compliance, CbD, for pharmaceutical compliance. The proposed approaches are logical, organized, well known and understood, and well accepted in the pharmaceutical industry.

The detailed QbD approach (13) to pharmaceutical development and manufacturing can be fundamentally conceptualized and simplified for application to CbD, as follows:

- **Objectives.** What are the target objectives and attributes of the specific quality system?
- **Critical parameters.** What may affect successful accomplishment of objectives?
- **Input variation and control.** What expected variation may cause problems and how can variation be controlled?
- **Ongoing maintenance and management.** How will the objectives be monitored, maintained, and improved?

These concepts may be easily applied to compliance by considering compliance as the “product” of quality systems and GMP activities just as pharmaceutical products are the objective of QbD. Thus we propose CbD according to the approach of QbD.

**CbD Objectives**
The CbD compliance objectives provide comprehensive expectations and critical attributes for each quality system. Just as a target product profile and critical quality attributes are determined for a product being developed, compliance objectives and attributes are determined for a quality system. For example, one of the components of the quality system is the annual product review (APR) program. Quality attributes of this program may include reviews in which high-risk products are reviewed quarterly and lower-risk products are reviewed at a lesser frequency during the regulatory year. Only certain high-risk quality attributes of products (e.g., dissolution) may be more frequently reviewed. Attribute data may be control charted and trends evaluated. Other quality attributes of the APR program should include reviews of non-conformances, deviations, and other events. Whenever a limit of
a CbD attribute is exceeded (for example, quarterly product reviews for a high-risk product not completed as required), a non-conformance notice would be issued. Periodic review of CbD non-conformances would provide a qualitative and quantitative measurement of system compliance performance.

Clearly defining and documenting the fundamental objectives and quality attributes of a quality systems program should not be judged to be an unnecessary task. A 2009 FDA warning letter (22) indicated deficiencies in the investigation of several occurrences of particulate matter in various products; the cited firm did not appear to have clearly defined objectives for its investigation process including fundamental expected requirements such as extending the investigation to other products manufactured under the same defect circumstances. Another item in this warning letter addressed deficiencies in the firm’s stability program. In addition to non-compliance with written policy, the firm lacked written policy addressing other expected aspects of a stability program. Another item addressed deficiencies in the firm’s laboratory sample control procedure. Clearly specifying the objectives and compliance attributes for these quality systems could have helped avoid the problems identified in the warning letter.

**CbD Critical Parameters**

The CbD critical compliance parameters are activities that are essential to assuring systems objectives and quality attributes are accomplished. Just as critical process parameters directly affect the critical quality attributes of a product, parameters may affect accomplishment of compliance attributes for the quality system. For example in the production system, the ongoing training of employees involved in aseptic processes is critical to assuring acceptable sterile products and environmental conditions. Training of these employees would receive high priority and be assiduously tracked because this training is of critical importance to the aseptic process production system. Training of aseptic employees may be required to be completed within seven days of the target date, may require a proficiency examination, and may be repeated annually reflecting the high risk of these activities. Another example: A refrigerated storage area in the material system may operate between 2°C and 8°C for compliant performance. Whenever the limit of a compliance parameter is exceeded (e.g., training time limit overdue, refrigeration temperature limit exceeded), a non-conformance notice would be issued to provide a qualitative and quantitative measure of system performance.

**CbD Variable Control Strategy**

The CbD input variable control strategy identifies variables the may affect compliance for a quality system and provides a method to control these variables. For example, failure of refrigeration equipment would cause failure of a cold temperature storage area. This occurrence could be mitigated by continuous monitoring of the temperature in the area and an immediate automatic alarm notification to department management whenever the target temperature range limit is exceeded. Any compliance activity performed completely by humans, such as manual cleaning processes, has innate variation. CbD would evaluate all product-contact equipment cleaning processes, identify fully manual processes, assure that personnel performing manual cleaning were appropriately trained, and monitor non-conformances associated with manual cleaning.

**CbD Maintenance And Management**

CbD ongoing monitoring and maintenance activities that contribute to continuing the success of the quality system include instrument calibration programs in the stability area, preventive maintenance programs on manufacturing equipment, and so on. The review of past performance and corrective action and preventive action (CAPA) experiences should lead to compliance system improvements to correct identified problems or enhance controls. For example, a commitment to install PAT on a purified water system would significantly improve performance of this equipment and ensure operational compliance. Non-conformances on systems supporting but not directly related to product manufacturing (e.g., purified water) may not receive sufficient visibility to be adequately addressed.
**Associated Concepts—Risk Analysis And PAT**

Risk analysis and PAT are associated concepts that are recommended for use in conjunction with QbD. These same concepts should be applied to compliance applications in CbD.

ICH Q9, *Quality Risk Management* provides several applications of applying risk analysis to compliance activities. Some of these include equipment, utilities, and facilities; preventive maintenance and calibration; training; change control; and other activities not directly associated with product manufacturing. Just as manufacturing activities are evaluated according to product risk and high risk activities receive primary focus, compliance systems should use this same approach.

Just as PAT is recommended for real time process control of manufacturing processes and minimizing variation, similar technology should be implemented as appropriate for compliance applications. For example, automated control system on United States Pharmacopeia (USP) purified water systems, use of bar coding to prevent drug-dispensing errors or in laboratory sample tracking systems, and other applications of new technology to enhance compliance is recommended. As with manufacturing processes, priority for implementation should be assigned to highest risk applications.

**Compliance by Design Implementation Approach**

Compliance by design should be implemented by a quality systems approach. This approach comprises evaluation of measures and activities as defined in the FDA quality systems categories as described in the FDA *Compliance Program Guidance Manual* (8). The quality systems approach would be consistent with approaches used by FDA in regulatory audits. For example, CbD applied to a material system would evaluate training and qualification of personnel, identification methods for components and closures, validation of supplier’s test records for incoming drugs, first-in-first-out control of components, control of the incoming material supply chain, and so on. This approach evaluates all related CGMP topics within the specified quality system.

CbD could also be applied to specific GMP components as described in 21 Code of Federal Regulations (CFR), such as all manufacturing equipment. This approach lacks the cross-functional integration inherent in quality systems.

**VALIDATION MASTER PLANS AND COMPLIANCE MASTER PLANS**

This paper proposes that documentation of the CbD program be contained in a compliance master plan.

The CMP is analogous to the current and well-accepted VMP. The concept of a CMP has been suggested by Nash (23) based on work of Borkar (24, 25). These authors proposed that six quality systems and 26 quality system elements form the basis for a CMP.

The VMP, as currently used, is actually a subset of that envisioned for the CMP, although having a somewhat different structure and organization. The VMP is essentially a compliance master plan for all validation activities conducted in the facility. We propose that the structure and content of the VMP be expanded to contain all compliance activities. The CMP is structured according to quality systems. This approach would list all quality systems individually as chapters of the CMP. Each system would describe its content and system objectives, compliance attributes, compliance parameters, input variables and control strategy, and continuous improvement commitments. Just as validation management is accountable for validation commitments in the VMP, compliance management would be accountable for compliance commitments in the CMP. Documentation of the facility CbD effort in the CMP would centralize compliance information in a manner useful for internal reference and regulatory audit. A CbD program documented in a CMP would demonstrate a definite organization commitment to compliance consistent with FDA and ICH expectations. Table I provides a suggested CMP table of contents indicating section titles according to a quality systems structure. Table II describes the specific content of a quality system chapter using the QbD general concept.

The CbD/CMP proposal may be implemented by building on current quality systems programs and validation VMP content that already exists at the manufacturing site. FDA has been auditing according to the quality systems approach for several years,
so industry should already be thinking by a systems approach. Industry may already have functional structures and documents organized according to quality systems. Validation and validation master plans have been well established for many years. The VMP contains a listing of all equipment, facilities, utilities, associated control systems, products, cleaning methods, analytical methods, and related information at the site. This information may be directly transferred to a CMP with separation into the respective quality system. Transitioning to a CbD approach should not require extensive efforts, and will result in both direct and indirect improvements in the compliance program. QbD and the validation master plan are proven successes. These successful approaches are logical applications to assure and enhance success in compliance.

**BENEFITS—WHY IMPLEMENT CBD/CMP?**

There are several benefits to implementing the CbD/CMP approach to compliance. These include the following:

- Organized and comprehensive focus on compliance
- Cross-functional thinking
- Consistent cross-functional prioritized mitigation activities
- Variation identification and control strategy
- Centralized tracking of commitments
- Standardized audit expectations and documentation.

**Organized And Comprehensive Focus On Compliance**

The CbD/CMP proposal is intended to organize, focus, and enhance compliance performance in the same way that QbD provides an organized focus on formulation and process development to result in a successful commercial product. CbD/CMP should be operative throughout the system lifecycle. CbD requires a clear definition of system objectives and attributes for successful system performance. When system work is executed, CbD/CMP enables evaluation of system compliance performance. Improvements are identified, and management of corrective actions and improvement projects are facilitated. All strategies, approaches, and analyses are systematically and prospectively documented. There should be no uncertainty regarding objectives, key attributes, successful performance, and improvement commitments because these are clearly documented in the CMP.

**Cross-Function Thinking**

The CbD/CMP approach forces a cross-function approach to compliance performance. The 21 CFR subparts are organized as individual components of pharmaceutical manufacturing, similar to organizational silos. The FDA quality systems approach integrates these “silos” for inspection efficiency. The CbD approach to quality systems should break down orga-
nizational barriers and assure consistent compliance objectives, attributes, risk assessments, and other actions between functional areas.

**Consistent Prioritized Mitigation Activities Across Functions**

The CbD/CMP approach should also ensure consistency in organizational focus across related functions. Self-audits should be conducted according to risk, and subsequent mitigation activities should be similarly prioritized. For example, equipment used in a high-risk process should receive maximum attention regarding preventive maintenance and calibration, have undergone thorough and rigorous validation and qualification, receive heightened evaluation of changes in change control, have clearly detailed operating procedures, and be operated by the most well-trained personnel (i.e., all related and integrated functions should be reviewed for consistency in performance and control to demonstrate consistent compliance). Training of environmental personnel for aseptic areas should be much different than training of environmental people responsible for warehouse storage areas. Just as the CbD approach should ensure consistent quality objectives across function areas, it should also help with consistent focus on high-risk activities and mitigation of high-risk problems.

**Variation Identification And Control Strategy**

CbD/CMP requires prospective consideration of potential input variation and development of a control strategy to minimize potential compliance issues. In material systems, for example, a comprehensive review of material suppliers for natural products should indicate potential sources of highly variable material or circumstances where materials sources are actually unknown. Also in material systems, review of test results for incoming key excipients may indicate highly variable materials that are still within specifications but suggest heightened potential for future manufacturing problems. Proactive identification and prevention of potential problems will serve future manufacturing.

**Centralized Tracking Of Commitments**

The CbD/CMP approach provides centralized and consistent tracking of compliance activities and commitments. Compliance commitments may be documented in various systems within the organization (i.e., CAPA systems, internal audit tracking systems, external audit tracking systems, organization functional goals, individual department management goals, individual employee goals, project team goals, and so on). The CbD/CMP document is an organizational document with cross-functional approval that should serve as the primary resource for tracking information in the same manner that the VMP provides centralized tracking of validation commitments.

**Standardized Audit Expectations And Documentation**

The CbD/CMP approach provides a standardized, open, transparent, and structured approach to compliance. Organizations who implement the CbD/CMP approach will ultimately rely on this program for continuing status updates regarding compliance performance and projects in the organization. Updating of the CMP should be coordinated with management updates to provide a reasonably current status of compliance activities in the organization. Maintaining the CMP, including project commitment dates, keeps the organization in a continuing state of readiness for regulatory, contractor, internal, or other audits. Audits of suppliers who use the CbD/CMP approach will be greatly facilitated. Transparency of supplier compliance by use of a CbD/CMP approach should be a significant benefit to industry and regulatory agencies.

**Organization Commitment, Transparency, And Credibility**

An organization that embraces the CbD/CMP approach demonstrates a strong commitment to CGMP compliance. The CbD/CMP approach requires forethought, planning, execution, and an ongoing review of compliance performance. As more experience is gained, continuing improvements in compliance performance are expected. Ultimately a high level of compliance should be routinely maintained.
Documenting the CbD approach in the CMP requires transparency in the compliance effort. In 2010, FDA announced its intention to become more transparent (26). The FDA program describes several benefits of transparency including accountability, enhancing the work of the agency, and increasing credibility with the public. Implementing a CbD/CMP approach in a pharma organization should similarly facilitate organizational transparency regarding compliance. It should foster accountability, enhance the compliance work of the organization, and increase the credibility of the compliance effort with auditors and with employees responsible for performing the work of compliance.

Day-to-day compliance depends on the daily performance of employees. The CbD/CMP approach sends a clear message to employees that compliant performance is important. A 2008 interview with a regulation agency representative (27) describes instances of inadequate internal audits and self-inspection programs. Major and critical deficiencies quickly identified by the regulatory agency were not identified or corrected by the firms themselves. Another example cited in this interview involved inadequate audits or minimal qualification work done to evaluate contractors doing outsourced critical work. These observations suggest a marginal compliance attitude in the organization. In turn, this attitude is perceived by employees. Organization commitment, including transparency in performance, will positively impact the credibility of the compliance effort.

CONCLUSIONS
This commentary has proposed an organized, simple, and logical approach to pharmaceutical compliance. The concepts recently developed in the QbD initiative and associated strategies including risk analysis have been applied to develop compliance by design. Documentation of CbD is proposed in a compliance master plan modeled on the well-accepted validation master plan. The CMP would contain the CbD objectives, attributes, and other quality systems information at the manufacturing site. The CMP would also contain commitments and timelines for correction of deficiencies and continuous improvements as is common in the VMP.

The CbD/CMP approach provides an organized and focused approach to compliance. This approach should facilitate a proactive evaluation of compliance performance against compliance attribute standards. This approach requires a cross-functional systems orientation in the facility, fosters consistent prioritized mitigation activities, and standardizes the structure of compliance documentation. The proposed CbD/CMP approach provides advantages that should improve compliance performance, enhance efficiency, and positively impact the compliance effort in the organization.

An organization that embraces the CbD/CMP approach demonstrates a strong commitment to CGMP compliance. Documenting the CbD approach in the CMP requires transparency in the organization. Transparency fosters accountability, enhances the compliance work of the organization, and increase the credibility of the compliance effort with auditors and with employees responsible for performing the work of compliance.

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