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QbD: Quality By Design

Understanding and Implementing the FDA's Quality by Design Initiative for the Pharmaceutical Industry

MAY 29–30, 2008, RADISSON-PLAZA WARWICK, PHILADELPHIA, PA

Featuring Case Studies and Lessons Learned from Industry Experts!

- Facilitate Innovation and Continuous Improvement Throughout the Product Lifecycle
- Provide Regulatory Flexibility for Specification Setting and Post-approval Changes
- Streamline the Submission and Review Processes
- Use a Risk-Based Approach to Designing Performance Characteristics for the Operation Used for the Manufacture of Drug Products
- Understand the Regulatory Requirements for QbD

Featuring an In-Depth Pre-Conference Workshop:

IMPLEMENTING A QUALITY BY DESIGN (QBD) APPROACH

Fernando Muzzio, Ph.D.,

Professor of Chemical Engineering, Rutgers University

Featuring Representation From:

Novartis Pharmaceutical Corporation
Rutgers University
PAREXEL Consulting
Harpaz Consulting
Drumbeat Dimensions, Inc.

Biogen IDEC
DSM Pharmaceuticals, Inc.
BE&K Engineering
Shadle Consulting



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Thursday, May 29, 2008

8:30 *Chairperson's Welcome and Opening Remarks*

MORNING WORKSHOP

9:00 **Implementing a Quality By Design (QbD) Approach**

Fernando Muzzio, Ph.D., Professor of Chemical Engineering, Rutgers University

This talk focuses on developing a QbD approach for controlling dissolution performance of new and existing products. "Quality by design" is a methodology that generally relies on the development of predictive relationships (whether statistical or fundamental) between inputs (material properties, process parameters) and responses (product attributes) for product optimization and quality control. As an initial step, special attention is devoted to method error, which needs to be minimized in order to implement meaningful statistical process control. Fishbone diagrams and process charts are used to identify critical (key) material and process variables. Prior knowledge, supported by statistical methods, are used to develop predictive methods for minimizing the impact of material and process variability on product performance.

About your workshop leader:

Professor Fernando Muzzio is the director of the new National Science Foundation Engineering Research Center on Structured Organic Particulate Systems. The center focuses on Pharmaceutical Product and Process Design. FDA and 30 companies are currently partners. Professor Muzzio is a Professor of Chemical Engineering at Rutgers University. For the last 15 years, pharmaceutical product and process design has been Professor Muzzio's main research and educational focus. He is the author of over 150 peer-reviewed scientific articles, book chapters, and patents, and several hundred lectures at technical conferences, companies, and universities in areas relevant to the pharmaceutical industry.

12:00 *Luncheon*

1:30 **Understanding the FDA's Quality by Design Initiative for the Pharmaceutical Industry**
Barry (Bir) Gujral PhD, Coordinator, Process Analytical Technology, DSM Pharmaceuticals Inc.
Quality by Design is a systematic approach of achieving desirable quality by carefully evaluating all attributes

that characterize quality, from the early stages of development and through out the product lifecycle. The purpose behind FDA's Quality by Design initiative is that quality should be built into a product with a thorough understanding of the product and process by which it is developed and manufactured, along with a knowledge of the risks involved in manufacturing the product and how best to alleviate those risks. The successful Quality by Design implementation is based on detailed, science-based understanding of the chemical and mechanical properties of all elements of the proposed drug product in order to design a process that provides consistent product. At that point all the critical sources of process variability are identified, measured and understood in order to be controlled by the manufacturing process itself. The main objectives of Quality by Design Principles are:

- To facilitate innovation and continuous improvement throughout the product lifecycle
- To provide regulatory flexibility for specification setting and post-approval changes
- To streamline the submission and review processes

The predefined product aspects done by Quality by Design establishes a product vision which serves as a reference to arbitrate conflicting constraints, limit late stage changes, increase product quality and lower overall development and manufacturing costs. The resulting paybacks from Quality by design to the Pharmaceutical Industry will be significant. There will be reduced batch failure rates, reduced final product testing and lower batch release costs. Thus there will be lower operating costs from fewer failures and deviation investigations and an increased predictability of manufacturing output and quality. The raw material, WIP and finished product inventory costs will also be reduced. The Pharmaceutical industry will get faster tech transfer between development and manufacturing and faster regulatory approval of new product applications & process changes thereby fewer and shorter regulatory inspections of manufacturing sites.

These paybacks translate into significant reductions in working capital requirements, resource costs and time to value. These gains in turn pave the way for additional top line growth and to the availability of safe, effective, consistent and affordable medicines to the consumers.

2:15

Engineering Quality by Design: A Pharmaceutical Product Risk Mitigating Approach

Gamal Amer, Ph. D., Senior Director of Technology and Regulatory Compliance, BE&K Engineering

All human endeavors come with an associated risk. Risk, which is the probability of harm occurring and its severity, can be classified in several levels. The level of potential risk dictates the actions one needs to take to address it. Designing a drug manufacturing operation so as to minimize or eliminate such risk can be achieved using a systematic approach. Good Engineering Practices (GEP) and the principles of Quality by Design (QbD) represents the current FDA thinking to achieve such objectives. Applying QbD principals when engineering the facility and process (operation) for producing a drug product requires good scientific understanding of both the product's characteristics and the processing approach. Understanding the potential risks associated with the proposed operation requires utilizing Subject Matter Experts (SME) and risk analysis techniques. GMP principles must also be addressed by the eventual design thus ensuring process consistency.

QbD is not a new concept when it comes to Good Manufacturing Practice (GMP) compliance in drug manufacture. The principal has existed for a long time. It is what was always referred to as building quality in the process/product and not relying on after the fact testing. QbD in engineering is a systematic scientific risk based approach to designing performance characteristics for the operation used for the manufacture of drug products, so as to consistently meet specific objectives or quality attributes. Applying QbD while designing the operation for the manufacture of drugs is an effective way to ensure that the operation once constructed, will produce a product with the desired quality attribute and minimize the product's potential risks to the patient. Producing a quality, efficacious and safe product consistently while minimizing the risk to the public is the ultimate goal of drug manufacturers and regulators alike.

This presentation will begin by defining risk and risk levels based on FDA guidance and ICH Q9. Next we will review some of the potential risk to the drug products and hence to the public from the manufacturing operation. We will then define QbD, some of its basic principals, and discuss how they are applied when designing

a new drug manufacturing operation to increase product and process understanding, mitigate the risks to the public, improve process flexibility and allow for continuous quality improvement. A review of some of the tools used in QbD will also be discussed. Finally, we will briefly review other advantages that may accrue from applying QbD to the design, such as reduced environmental impact, and increased safety.

By attending this session you will learn:

- What is risk?
- How to identify, analyze, and evaluate risks and their potential impact?
- What QbD entails?
- What is needed for successful implementation of QbD?
- How to apply the QbD principals during the design of the drug production operation.
- How applying the principals of QbD mitigate risk to product quality?

3:00

Refreshment Break

3:15

Understanding the Regulatory Requirements for QbD

Daniel Harpaz, Ph.D, Harpaz Consulting

This presentation will discuss the rationale for the establishment of the QbD concept by ICH. Once we understand the background behind this concept we can apply it correctly. After the introduction of the GMP regulations the concept of process validation was expanded in the mid 1980s, and then came the concepts of Change Control and the Development Report to support the establishment of manufacturing process parameters for process validation.

With the introduction of GMP for the 21st Century the idea of Quality By Design was introduced, in practice it is no different that what was performed by the multinational pharmaceutical companies as part of product development cycle already in the 1970s.

4:00

Analytical Methods Development and Quality-by-Design

Paula J. Shadle, Ph.D., Principal, Shadle Consulting

This session will focus on selecting and developing analytical methods for new products and using a quality-by-design approach to assess potential assay technologies for their suitability for intended use.

You will learn how to:

- Define testing requirements for product and process intermediates

- Define method capabilities needed both during development and for commercial QC support
- Scope out cycle time and capacity requirements
- Map potential methods against your own expertise and available outsourcing alternatives

In this session, typical examples of analytical methods changed after licensure will be used to illustrate and define a proactive approach that relies on QbD. Common challenges for biopharmaceuticals include: potency assays, in which the most 'biologically relevant' test may have the least throughput and precision; microbiological testing having long incubation times, yet with real-time responses needed for effectiveness; and defining the business case for implementing PAT.

4:45 *Close of Day One*

Friday, May 30, 2008

8:30 **Quality by Design for the Analytical Chemist- A Proactive HPLC Methods Development Approach**

Rosario LoBrutto PhD, Group Head, Pharmaceutical and Analytical Development Novartis Pharmaceuticals Corp.

Quality by Design (QbD) concepts can be applied in process development, formulation development and analytical development. An approach to applying quality by design principles for the development, validation and transfer of analytical methods will be presented.

Chromatographic methods that are developed need to accurately quantify analytes with acceptable accuracy and precision while at the same time need to be robust and easily transferable to the production facility/CRO. In regards to analytical HPLC method development, various activities lead to the development of a final optimized method, which will be validated according to stage of development. The method development process can be broadly categorized into three spaces: knowledge space, design space, and control space. The knowledge space encompasses all considerations made, all experiments conducted, and all knowledge gained in the development of a method (ie column screening, pH screening experiments). The knowledge space forms the basis for delineating a design space within which one can modify the chromatographic variables (ie, gradient slope, temperature at a defined pH, buffer concentration) without significantly impacting the final quality of the method and all the

chromatographic figures of merit can still be met (Resolution of critical pairs, tailing factor, selectivity, etc). Although, methods executed anywhere within the design space will meet the desired system suitability criteria, in some cases the design space could be broad, and for practical purposes, one can define a control strategy, where the range of the chromatographic parameters are set for the final validated method.

Applying method optimization packages such as DryLab® and Autochrom (Advanced Chemistry Development) are efficient tools in optimizing and evaluating robustness of chromatographic methods leading to creation of the initial design space. The generation of resolution maps provides a clear representation of a multi-dimensional design space and provides a rapid assessment in regards to method robustness. The inherent challenges with creation of the resolution maps are the tracking of the components between the various chromatographic runs. Advances in the area of peak tracking using both diode array and LCMS will be discussed. The design space can be further fine tuned by the implementation of Design of Experiments (DOEs) to better understand the relationship/interactions for the 1) chromatographic variables and 2) sample preparation steps. Benefits of attending this session include:

- Apply Quality by Design principles to the design and evaluation of analytical methods
- Provide practical examples of knowledge, design and control spaces for chromatographic methods.
- Understand the role of method optimization packages for the creation of the design space
- Incorporation of "Design of experiments" in the method development strategy to further define the design space and the control strategy.

9:15 **Strategies for Managing Organizational and Technology Change in a QbD-Centric Environment**

Martin E. Zuzulo, Vice President, PAREXEL Consulting

The pharmaceutical industry has witnessed upheavals in how pharmaceutical product development is conducted. The increase in regulatory guidance around QbD, product complexity, and rapidly changing market forces observed in the pharmaceutical industry have also spawned a massive challenge: managing the organizational, process and technological change associated with increasing Quality by Design efforts.

Despite the significant benefits which can be realized from implementing a QbD-centric organization, the adverse effects of these changes can range from increased cycle time, organizational resistance and inability to capture key process and product understanding.

This session addresses the types of change we are observing in the QbD "marketplace" and strategies your organization can take in effectively managing them. It will take advantage of several perspectives, ranging from a marketplace "level set" to views by pharmaceutical and other organizations who are already involved in varying degrees of change impact resulting from QbD efforts.

10:00 *Refreshment Break*

10:15 **Quality by Design and Process Understanding are Complimentary**

*Barry (Bir) Gujral, Coordinator,
Process Analytical Technology,
DSM Pharmaceuticals Inc.*

Quality by Design is the ability to describe and justify why proposed design features deliver with confidence the intended quality and not awaiting test results to be submitted in a post approval supplement. Once the properties of the drug product components are understood, the processing variables that control the relevant properties are identified. Identification of these variables requires a multivariate approach. PAT implementation involves the design of manufacturing processes based on a thorough scientific understanding of the solid-state properties and stability of the components of the drug product at critical points throughout manufacturing. Then, measurement and control of the critical parameters integrates a broad spectrum of analytical technologies interfaced to production plant control networks and incorporated into standard procedures.

For Process Understanding, the Critical Process Parameters (CPP) driving variability in the Critical Quality Attributes (CQA) are identified and understood during process development so that they can be measured and controlled in real-time during the manufacturing process. It requires a culture of continuous improvement without the need for regulatory intervention to approve changes, and teamwork of process development and manufacturing along with deployment of appropriate enabling technologies. This teamwork will have the potential to drive the adoption of better practices and sustain the business benefits of higher levels of

process predictability and quality compliance across the entire manufacturing network. Design Space depends on fully utilizing the prior knowledge and experience of the process understanding of manufacturing teams. These analyses monitor, identify and correlate the relationships between CPPs and CQAs under the well controlled full-scale operating conditions being used during commercial manufacturing. We can't Design Quality into Pharmaceutical products without Process Understanding. That concludes that Quality by Design and Process Understanding go side by side or complimentary to each other.

11:00 **The Role of QbD in Process Validation**

*Tim Fields, President,
Drumbeat Dimensions, Inc.*

Quality by Design and Validation use the knowledge gained through the application of scientific approaches and quality risk management to life of a product from development through commercial production. The principles of QbD are changing the approach to validation and continuous process monitoring.

While traditional validation has focused on the first three batches produced to demonstrate process knowledge and control, QbD principles focus attention on the process knowledge gained during development and throughout the product lifecycle. This presentation will explore the role of QbD in process validation and compare the traditional validation approach to approaches that use QbD principles.

Benefit Points:

- Provides an overview of the basic principles of QbD
- Suggest potential new process validation approaches
- Explores use of continuous validation based on QbD principles
- Incorporates elements of process validation, QbD, Process Analytical Technology, and Real-Time Release

11:45 *Luncheon*

1:15 **Using QbD to Reduce QC Testing and its Associated Costs**

*Paula J. Shadle, Ph.D., Principal,
Shadle Consulting*

This session will explore strategies for streamlining QC testing and reducing cost for commercial products, using QbD as an approach. In this session you will learn how to:

- Identify testing that is non-value added
- Assess risk of reducing testing via good science, regulatory considerations, and statistical approaches
- Develop justifications for regulatory authorities

QC costs are often neglected in business cost models, yet can have significant impact both in direct per-lot costing and in increased release cycle times for biopharmaceuticals. Once a product is licensed, making changes is costly and challenging; coupled with concerns about risk, the result may be a bloated QC testing strategy that includes tests known to not be stability-indicating or useful to detect non-conforming product. This session will utilize Quality-by-Design as a means to locate and reduce testing costs whilst maximizing the collection and interpretation of useful data.

2:00

Case Study: Techniques to Characterize Complex Raw Materials for Biopharmaceuticals

Maureen Lana PhD, Principal Scientist, Biogen Idec

With the advent of high yield cell-culture processes, more demand than ever is being put on raw material supplies in order to maintain cells in high-density cultures. This increased demand for raw materials adds urgency to the need to be able to predict cell-culture performance from raw material properties and feed-stream analysis. We describe multivariate HPLC, NMR and MS techniques and how they may be applied in a robust, timely manner to analyze complex raw materials.

Hydrolysates are commonly used additives for cell culture media and feed solutions. Naturally derived hydrolysates contain many small and large molecules that can affect cell-culture characteristics in different ways. Might some of these compounds limit the growth of cells in a bioreactor just as the essential nutrients found in the same material promote growth? This presentation describes recent advances in our laboratory to identify, understand and control multiple chemical factors present simultaneously in media additives derived from natural sources. Data processing techniques and strategies will be described for fingerprint results obtained using HPLC, NMR, and MS.

2:45

Refreshment Break

3:00

Effective QbD For APIs

Daniel Harpaz, PhD, Harpaz Consulting

This presentation will discuss the use of Design of Experiments (DOE) for the manufacturing of New Chemical Entities from the one kg. laboratory to pilot-plant and finally to commercialization. The objective of performing DOE is to define the process parameters as

they relate to API quality. Topics covered:

- API Quality attributes:
 - Chemical
 - Physical
- Development of synthetic route
- Process development in pilot-plant
- Identification of Critical process parameters

3:45

Achieving ICH Q10 Objectives in Chromatographic Analytical Method Transfer

James K. MacNamara, Associate Director of Analytical Services, Genaera Corporation

- Chromatographic methods Supporting Pharmaceutical Product Development
 - API assay, purity, residual solvents, Ion Chromatography and chiral HPLC
 - Excipient compatibility (typically API assay/purity)
 - Drug product assay, purity
 - Methods demonstrate product realization
 - Establish product state of control
 - Optimization for continuous improvement
 - Preparing the receiving laboratory for analytical method transfer
 - Responsibility for successful transfer part of oversight of outsourced activities
 - Sponsor, and/or transferring laboratory responsible for successful process
 - Coordinating communication and document assessment between laboratories
 - Establish receiving laboratory method familiarity with empirical "scout" work
 - Determining receiving laboratory method adherence by scout data assessment.
 - Acceptance criteria based on "Critical Process Parameters" (CPP) established to support "Critical Quality Attributes" (CQA).
 - Method transfer protocol
 - Protocol Execution and Control Strategy
 - Executed Protocol/Transfer Report
 - Example of using Method Transfer to Support QbD Process Improvement
 - Determining CPP's during process 'upset'
 - Opportunity to introduce "PAT" into process
 - HPLC method improvement and transfer in support of IPC testing
 - Case study example of "in specification impurity" being unacceptable
- Participants will review method transfer protocol in support of In Process Control testing.

4:30

Close of Conference



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