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ENGELBERG CENTER for Health Care Reform at BROOKINGS

Discussion Guide

Measuring Pharmaceutical Quality through Manufacturing Metrics and Risk-Based Assessment

Background

Issues in pharmaceutical manufacturing have the potential to significantly impact patient care, as failures in quality may result in product recalls, drug shortages, and harm to patients.[1,2,3] In a recent report, the Government Accountability Office (GAO) found that approximately 40% of drug shortages resulted from quality concerns, with shortages continuing to rise in recent years.[2] Failures in manufacturing quality often come about through breakdowns in manufacturing processes, facilities, or issues associated with the "quality culture" of an organization. Recent legislative actions and regulatory reforms have provided additional tools that regulators and manufacturers can use to help ensure that product manufacturing is conducted safely, predictably, and at a high level of quality. Among these tools are vehicles for the more efficient and effective utilization of manufacturing quality metrics. The broad and uniform collection of metrics could provide various stakeholders – from industry to regulators – with greater insight into the state of quality at a given manufacturing facility, and allow stakeholders to better anticipate and address quality issues. As quality failures in pharmaceutical manufacturing have implications for a wide range of stakeholders, addressing those problems and implementing new solutions will require the support and collaboration of multiple stakeholders, including manufacturers, purchasers, health systems, and government agencies.

Regulatory Oversight of Pharmaceutical Manufacturing

Current Good Manufacturing Practices (cGMP)

As part of its mission to protect and promote public health, the U.S. Food and Drug Administration (FDA) maintains and enforces regulatory requirements for pharmaceutical manufacturing, known collectively as Current Good Manufacturing Practices (cGMP).[4] These regulations represent the minimum standard that manufacturers must meet in terms of the facilities, methods, and controls used to manufacture, process, hold, or package pharmaceutical products.[5] FDA regularly conducts inspections of pharmaceutical manufacturing facilities to ensure full compliance with cGMP regulations. Such inspections are carried out both as part of the approval process of new or generic drugs, as well as

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[1] Wang, B., et. al. *The Epidemiology of Drug Recalls in the United States.* Arch Internal Medicine. Volume 172 (no. 14), July 23, 2012

[2] U.S. Government Accountability Office. *Drug Shortages: Public Health Threat Continues Despite Efforts to Help Ensure Product Availability*. February 2014. Retrieved February 12, 2014, from: http://www.gao.gov/assets/670/660785.pdf

[3] Gogineni, K., et. al. *Survey of Oncologists about Shortages of Cancer Drugs*. New England Journal of Medicine. 2013; 369:2463-2464. December 19, 2013. Retrieved January 24, 2014 from: http://www.nejm.org/doi/full/10.1056/NEJMc1307379?query=TOC

[4] Code of Federal Regulations. Title 21--Food And Drugs Chapter I--Food And Drug Administration Department Of Health And Human Services Subchapter C--Drugs: General. PART 210 Sec. 210.1 (a). Retrieved April 9, 2014, from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=210.1

[5] Ibid.

throughout the lifecycle of the product following approval, usually on a biennial basis.[6] Failure to comply with cGMP can result in regulatory actions taken by the agency, including warning letters, seizure of a product, recalls, and fines.[7,8] In an effort to further enhance the regulation of pharmaceutical manufacturing, FDA launched the Pharmaceutical Quality for the 21st Century initiative in 2002. As part of this program, the agency identified a number of guiding principles that would help to modernize the regulation of manufacturing processes, including the adoption of a risk-based orientation, science-based policies and standards, integrated quality systems orientation, international cooperation, and strong public health protection.[9]

In addition to these US-specific regulatory initiatives, FDA is engaged in efforts to harmonize the scientific and technical principles adhered to by the regulatory bodies and pharmaceutical manufacturers of the European Union and Japan through the International Conference on Harmonisation (ICH). As part of these efforts, the ICH has developed and implemented nearly 60 joint guidelines and standards on drug development, manufacturing, and distribution, many of which relate to manufacturing quality.[10] Regulatory guidance has also been developed by organizations such as the World Health Organization (WHO), which provides member states with a basis for developing cGMPs within their own regulatory frameworks.[11]

Quality by Design (QbD)

In an effort to further promote quality product manufacturing, FDA has moved to integrate quality by design (QbD) concepts within its regulatory guidance and oversight. QbD provides a framework to ensure that process and product quality manufacturing is conducted in a systematic, risk-based manner for manufactured products.[12,13] These concepts were initially introduced within FDA's 2004 regulatory guidance for Process Analytical Technologies, and QbD has since been incorporated within additional guidances, as well as ICH guidelines pertaining to pharmaceutical development, quality risk management, and pharmaceutical quality systems (known also as Q8, Q9, Q10 and Q11 guidelines, respectively).[14,15,16,17,18] In 2011, the European Medicines Agency (EMA) and the FDA launched a pilot

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[6] U.S. Food and Drug Administration. (February 2012). *Compliance Program Guidance Manual Program*. Retrieved April 9, 2014, from http://www.gmp-compliance.org/guidemgr/files/7356-002_FINAL.PDF

[7] U.S. Food and Drug Administration. (May 2013). *Facts about Current Good Manufacturing Practices (cGMPs)*. Retrieved April 9, 2014, from http://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm

[8] U.S. Food and Drug Administration. *FDA Fiscal Year 2013 Enforcement Statistics*.

[9] U.S. Food and Drug Administration. (September 2014). *Pharmaceutical cGMPs for the 21st Century —A Risk-Based Approach*. Retrieved April 9, 2014, from http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/UCM176374.pdf

[10] International Conference on Harmonisation. (2014). Quality Guidelines (page). Retrieved April 9, 2014, from http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html

[11] World Health Organization. (December 2006). *Quality Assurance of Pharmaceuticals: a Compendium of Guidelines and Related Materials*. Volume 2, second update addition. Retrieved April 9, 2014, from http://www.who.int/medicines/areas/quality_safety/quality_assurance/QualityAssurancePharmVol2.pdf

[12] Rathore, A. and H. Winkle. *Quality by Design for Biopharmaceuticals.* Nature Biotechnology. *27, 26 - 34 (2009) doi:10.1038/nbt0109-26.*

[13] Arora, T., et. at. *Quality by Design for Biotechnology Products*. (December 2013). BioPharm International. Retrieved April 9, 2014, from http://www.processdevelopmentforum.com/articles/quality-by-design-for-biotechnology-productspart-1/

[14] Ibid.

program to conduct parallel assessments of applications to help ensure the consistent implementation of QbD in manufacturing quality and CMC.[19] The integration of QbD within regulatory guidance represents an important step taken by the agency to facilitate quality control and improvement in manufacturing.

Beyond cGMPs: Quality as a Function of Drug Manufacturing Quality Control, Product Knowledge, and Process Enhancements

In recent years, FDA's approach to quality oversight has evolved to a regulatory approach which emphasizes production quality control and continuous product and process enhancements. Recent developments, including increases in drug shortages, recalls, and the agency's broader shift towards a risk-based approach to regulation have provided an impetus to further these transformations. FDA is now in the process of undertaking major organizational and work process reforms relating to pharmaceutical quality.[20] Through these initial steps, FDA will provide a single, agency-wide voice for ensuring that high-quality medicines are available for the American public by anticipating quality problems before they happen, establishing consistent quality standards and clear expectations for industry, and emphasizing the use of quality metrics to anticipate and address quality issues which result in drug shortages and recalls, promote continuous quality improvement in manufacturing, and ensure product quality without extensive regulatory oversight.

Office of Pharmaceutical Quality (OPQ)[20]

Among the organizational and work process reforms currently underway at FDA is the establishment of an Office of Pharmaceutical Quality (OPQ), which will be tasked with the implementation of integrated, team-based assessment for products, manufacturing processes, and facilities. OPQ will develop standards and carry out inspections, reviews, and surveillance across all pharmaceutical products, including brand-names, generics, and over-the-counter (OTC) products. Within OPQ, the agency has proposed the creation of an Office of Surveillance, which will conduct continuous monitoring and assessment of the state of quality of drug products and facilities which supply the U.S. market. This office will analyze a wide variety of quality-relevant information—including data from regulated manufacturers—and will manage FDA's evolving approach to quality surveillance inspections. While the

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[15] U.S. Food and Drug Administration. (September 2004) *Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*. Retrieved April 9, 2014, from http://www.fda.gov/downloads/Drugs/Guidances/ucm070305.pdf

[16] International Conference on Harmonisation. (August 2009). *Pharmaceutical Development Q8 (R2)*. Retrieved April 9, 2014, from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf

[17] U.S. Food and Drug Administration. (May 2007). *Q10 Pharmaceutical Quality System*. Retrieved April 9, 2014, from http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128031.pdf

[18] U.S. Food and Drug Administration. (November 2012). *Guidance for Industry: Q11 Development and Manufacture of Drug Substances*. Retrieved April 21, 2014 from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM261078.pdf

[19] European Medicines Agency. (August 2013). *EMA-FDA Pilot Program For Parallel Assessment Of Quality-By-Design Applications: Lessons Learnt And Q&A Resulting From The First Parallel Assessment*. Retrieved April 9, 2014 from http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/08/WC500148215.pdf

[20] Wesdyk, R. *FDA/CDER's Evolving Approach to Quality and the Use of Metrics* (Presentation). 14 March 2014. Retrieved April 10, 2014 from http://xavierhealth.org/wp-content/uploads/3.-Wesdyk_Next-Steps-for-the-CDER-Challenge.pdf

office is currently in the development process, it is expected to play a large role in implementing FDA's evolving approach to risk-based drug quality oversight.

The Food and Drug Administration Safety and Innovation Act of 2012

The FDA's broader shift toward risk-based oversight is driven in part by the passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, which includes several provisions aimed at improving the FDA's approach to regulating drug quality. In light of the fact that an increasing share of drug products are manufactured (either in whole or in part) abroad, the legislation requires the agency to increase its inspections of foreign manufacturing facilities, with the ultimate goal of achieving parity of inspection frequency between domestic and foreign sites by 2017.[21] It also directs the agency to replace its biannual inspection system with a risk-based inspection system, which will require the agency to factor known risks—such as compliance history, past recalls, and prior inspection frequency—into its decision-making process for scheduling inspections and allocation of inspection resources. In order to support the risk-based assessment process, as well as streamline the on-site inspection process, FDASIA also authorizes FDA to collect records from manufacturers in advance or in lieu of facility inspections.[22] These new regulatory tools will enhance FDA's ability to determine which manufacturers have the highest risk of experiencing quality failure, respond accordingly through regulatory activities, and ultimately mitigate their effects or prevent those issues from arising in the first place.

Mitigating and Preventing Drug Shortages

The recent increase in critical drug shortages has provided further impetus to reform FDA's approach to oversight. Drug and biologic shortages pose a serious threat to patient care, and can result in treatment delays or the use of alternative therapies that are less effective or more expensive.[3,23] While shortages can result from a number of market forces (e.g., increased demand, industry consolidations), manufacturing disruptions are most frequently a result of failures in manufacturing quality.[22,24] Pharmaceutical and biologic manufacturers that fail to maintain acceptable levels of quality in their facilities or products can face regulatory penalties, including temporary shutdowns for facility upgrades, suspension of manufacturing, and halted distribution of products.[25] These short- and long-term disruptions can impact the number of drug and biologic products available to patients and providers.

FDA has been able to address these issues more comprehensively since the passage of FDASIA. For example, manufacturers are now required to alert the FDA of potential shortages, and the agency can exercise greater discretion in terms of how it balances the risks associated with a drug shortage versus the risks of keeping a drug on the market that may not meet quality requirements. However, more work is needed to effectively manage the effects of shortages, as well as prevent them from occurring. In February, 2013, the FDA Drug Shortages Task Force solicited stakeholder input on a range of issues,

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[21] U.S. Food and Drug Administration. (April 2014). *Generic Drug User Fee Amendments of 2012*. Retrieved April 9, 2014 from: http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm

[22] U.S. Food and Drug Administration. *Strategic Plan for Preventing and Mitigating Drug Shortages*. October 2013. Retrieved April 9, 2014 from: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf

[23] U.S. Food and Drug Administration. *A Review of FDA's Approach to Medical Product Shortages*. October 2011. Retrieved January 14, 2014 from www.fda.gov/DrugShortageReport

[24] U.S. Government Accountability Office. *Drug Shortages: FDA's Ability to Respond Should Be Strengthened*. November 2011. Retrieved from: http://www.gao.gov/assets/590/587000.pdf

[25] U.S. Food and Drug Administration. *FDA Inspections, Compliance, Enforcement, and Criminal Investigations, "FY 2011 Enforcement Activity."* Retrieved January 29, 2014 from: http://www.fda.gov/ICECI/EnforcementActions/ucm247813.htm

including the underlying causes of drug shortages, possible preventive actions, and the potential role of manufacturing quality metrics in informing FDA's oversight process.[26] FDA's commitment to mitigating drug shortages and ensuring product quality are closely aligned, and drug shortages will remain an important consideration in the development of manufacturing quality metrics going forward.

Developing Manufacturing Quality Metrics for Use within Risk-Based Oversight Framework

The collection and analysis of standardized manufacturing quality metrics can support FDA's overall approach to quality regulation in several key ways. Metrics can provide more objective information on how well a given manufacturer is managing its quality systems. Closer scrutiny of these metrics can help promote positive firm behaviors and a corporate culture of responsibility for quality, and may lead to rewarding the achievement of quality without extensive regulatory oversight. Paying attention to quality metrics could also help FDA to identify products at higher risk of shortage or recalls, which may in turn help to reduce their frequency. Quality metrics could also inform the agency's approach to risk-based inspection, as mandated under FDASIA. Metrics data might help FDA to stratify manufacturing sites according to quality risk, devote additional resources toward those sites with a higher risk profile, and reduce the inspection burden placed on high-quality performers. More broadly, metrics could contribute to ongoing FDA efforts to increase the visibility of drug quality. The agency already makes certain information about manufacturing problems publicly available on its website, but this information is related primarily to recalls, safety alerts, and the regulatory compliance status of a given manufacturing site, which provides limited insight on the state of quality of a given manufacturer's products or facility operations.[27,28]

This lack of market visibility regarding the state of quality has potential implications for patient safety, particularly as it relates to drug shortages. Currently, pharmaceutical companies do not compete based on their relative levels of manufacturing quality, and some have suggested that a broad-based quality metrics program that allows manufacturers to promote and publicize their own data could help shift the incentives towards competition based on manufacturing quality.[29] In particular, stakeholders such as wholesalers, group purchasing organizations, and insurers could use manufacturer-supplied quality metric data or quality rankings to inform their drug purchasing and pricing negotiations, thus providing incentives for manufacturers to develop and maintain better quality systems and processes.[2] However, others counter that these organizations have limited experience in interpreting manufacturing quality metric data, and that public reporting could paint a misleading picture of the quality of a given manufacturer's products.[30]

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[26] U.S. Government Printing Office. *Food and Drug Administration Drug Shortages Task Force and Strategic Plan; Request for Comments*. Federal Register, FDA-2013-N-0124. 12 February 2013. Retrieved April 1, 2014 from: https://federalregister.gov/a/2013-03198.

[27] U.S. Food and Drug Administration. *Inspections, Compliance, Enforcement, and Criminal Investigations: Enforcement Actions* (webpage). Retrieved from: http://www.fda.gov/iceci/enforcementactions/ucm222557.htm on April 3, 2014.

[28] U.S. Food and Drug Administration. *Safety: Recalls, Market Withdrawals, & Safety Alerts* (webpage). Retrieved April 14, 2014 from http://www.fda.gov/Safety/recalls/default.htm.

[29] Haninger, K, A. Jessup, K. Koehler. *Issue Brief: Economic Analysis of the Causes of Drug Shortages.* Office of the Assistant Secretary for Planning and Evaluation. October 2011. Retrieved April 22, 2014 from: http://aspe.hhs.gov/sp/reports/2011/drugshortages/ib.pdf

[30] See, for example, the comments submitted by Hospira and AstraZeneca in response to FDA's request for public comment on its Strategic Plan to Combat Drug Shortages: http://www.regulations.gov/#!documentDetail;D=FDA-2013-N-0124-0100 and http://www.regulations.gov/#!documentDetail;D=FDA-2013-N-0124-0032.

Selecting, Defining, and Interpreting Quality Metrics

The extent to which standardized quality metrics can contribute to the FDA's goals will depend largely on which metrics are selected, how they are defined and collected, and how they are interpreted. Pharmaceutical manufacturers currently use a broad range of quality metrics to measure internal performance within their respective organizations. These metrics are typically selected based on several key factors, including the nature of the product being manufactured, the systems and processes in place at a given site, and the manufacturer's overall approach to quality assurance and improvement. As such, there can be variation between manufacturers—and sometimes between different sites operated by the same manufacturer—in terms of how metrics are defined, collected, and assessed.[31] Collecting and reporting a standardized set of metrics to an external audience in a way that will allow for product-to-product or site-to-site comparisons may require changes to existing systems and processes. However, it is also noted that there are existing private programs that collect voluntarily reported, standardized quality metrics from a large and varying array of manufacturing sites, which allows participating manufacturers to benchmark their performance against that of other manufacturers. The program under development is an extension of that existing successful construct.[32]

Since early 2013, FDA has sought public input on which metrics it should consider collecting, and how to use and evaluate these metrics as part of its risk-based decision-making process. In response, several industry stakeholder groups have worked to identify a potential metric set, as well as develop recommendations for their interpretation.[33,34] The resulting proposals overlap in certain key respects. Most, for example, recommend beginning with either a pilot collection program or a phased approach to implementation, using a small number of metrics that are commonly used and easier to collect and report. Several proposals note that these more common metrics are 'lagging' indicators' (i.e., they provide information on past performance), and that 'leading' indicators (i.e., predictive of future performance) would be more useful for risk assessment. However, such metrics would be significantly more difficult to collect, and more work would be required before they could be implemented as part of FDA's quality oversight process. Several metrics are also common to more than one proposal, though the specific definitions vary slightly. See Table 1 below for a list of the metrics agreed to by a majority of the contributing stakeholders.

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[31] Consumer Healthcare Products Association (CHPA). Comments on quality metrics to assist FDA in identifying objective measures of product quality and plant operations performance for the purpose of supporting risk-based inspection approaches. Submission to FDA, December 19, 2013. Retrieved April 14, 2014 from: http://www.chpa.org/12_19_13_ProductQuality.aspx.

[32] Two such examples include the POBOS Benchmarking Program operated by McKinsey (http://solutions.mckinsey.com/pobos/) and the Operational Excellence in the Pharmaceutical Industry, based at the ITEM Institute of Technology Management at the University of St.Gallen. (http://www.opexbenchmarking.com/OPEX_files/PharmaOPEX2_0.pdf)

[33] Parenteral Drug Association. Points To Consider: Pharmaceutical Quality Metrics. (2013). Retrieved April 14, 2014 from: http://www.pda.org/pdf-1/PDA-Pharmaceutical-Quality-Metrics.aspx

[34] International Society for Pharmaceutical Engineering (ISPE). (December 2013) ISPE Proposals for FDA Quality Metrics Program – Whitepaper. Retrieved April 14, 2014 from: http://www.ispe.org/quality-metrics-initiative

Table 1: Consensus metrics proposed by stakeholders

Metric	Possible definition
Lot rejection rate	Number of lots rejected/ Number of lots attempted
Product Quality Complaint Rate	Number of quality complaints/ (Number of units released/1 million)
Confirmed OOS rate	Number of confirmed OOS/ Number of release tests conducted
Recall rate	Number of product recalls / Number of lots released

The proposals also note that quality metrics alone provide an incomplete picture of the state of quality control at a given site, and that they must be analyzed within a broader context. Factors such as the number and type of products manufactured at a particular site, the scale of the operation, and the complexity of the manufacturing process also have important implications for evaluating quality performance and the level of risk associated with a particular product or site. In light of this, most recommend that the FDA draw on information that is already available to the agency through other reporting mechanism. Data from the Field Accomplishments and Compliance Tracking System, for example, can provide supplementary qualitative information from past FDA inspections, while information on the type of facilities operated by a given manufacturer can be obtained from the electronic Drug Registration and Listing System (eDRLS).[35,36] External supplementary data sources might also include the Pharmaceutical Inspection Cooperation Scheme and IMS.[37,38] In addition to providing important contextual information, relying on these existing data sources will reduce the reporting burden on industry.

Several of the proposals also note key issues the will require further exploration. In particular, further discussion is required over the appropriate level at which to report metrics (e.g., per product, per site, or per manufacturer), how these metrics should be defined, and whether they should be reported and analyzed as an absolute value or on a trending basis. An additional challenge that will require further discussion is how to prevent gaming behavior (i.e., creating a false or misleading picture of the quality at a given firm by manipulating the data underlying the metric) and other unintended consequences of a reporting program. More broadly, there are ongoing questions as to how best to interpret quality data (both the metrics and additional contextual data available to FDA) as part of a risk-assessment process, as well as how and to what extent metric data should be made public.

Meeting Objective and Discussion Questions

In light of these issues, the Engelberg Center for Health Care Reform at the Brookings Institution, in cooperation with FDA, is holding an expert workshop that will focus on questions related to selecting,

[35] U.S. Food and Drug Administration. *Field Science and Laboratories: Laboratory Manual, Volume III - 2.1* (webpage). Retrieved April 14, 2014 from: http://www.fda.gov/ScienceResearch/FieldScience/ucm174181.htm

[36] U.S. Food and Drug Administration. *Drug Registration and Listing System (DRLS & eDRLS)* (webpage). Retrieved April 14, 2014 from: http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/drugregistrationandlisting/default.htm

[37] The Pharmaceutical Inspection Cooperation Scheme provides a forum for regulatory authorities to share resources, provide training to inspectors, and coordinate across borders on matters relating to GMP. More information can be found here: http://www.picscheme.org/pics.php

[38] IMS collects a range of pharmaceutical market data, and can provide information on product- and firm-level market share.

defining, and implementing a common set of manufacturing quality metrics. This workshop will provide an opportunity for stakeholders to discuss the broad objectives of the FDA's quality metrics program, identify and explore the opportunities and challenges associated with their collection and use, and considerations in exploring the next steps in their implementation. The workshop is divided into nine sessions over two full days. Representatives from FDA will begin the discussion on Day 1 with an overview of the agency's recent efforts in this area, as well as a summary of the work that has already taken place. In the ensuing sessions, a few lead discussants will help to frame the conversation through brief remarks, which will then be followed by an open discussion among participants in the room. On Day 2, moderated discussion will continue, and will focus on developing consensus around a draft set of metrics, their definitions, the implementation process, and potential approaches to analysis and use of the metrics. Further details on the structure of these sessions are provided below.

Measuring Pharmaceutical Quality through Manufacturing Metrics and Risk-Based Assessment

DAY ONE

Session One: Pharmaceutical Quality Metrics: Program Goals and Stakeholder Feedback

- What are FDA's goals in collecting pharmaceutical manufacturing quality metrics? Are these goals reasonable and appropriate, and do they align with other stakeholders?
- What quality metrics have been proposed by manufacturers and manufacturing associations? What are the areas of consensus, and what potential gaps still remain in terms of capturing overall quality at a site or manufacturer level?
- What lessons can be learned from previous experience using quality metrics to benchmark manufacturing performance?

Session Two: Reflecting on the Consensus Set of Metrics and Approaches

- What are the strengths and weaknesses of the consensus set of metrics?
- How well do these metrics align with the goals and objectives of the FDA?
- What additional metrics might be considered to address the potential gaps?

Session Three: Exploring the Use of Metrics in Purchasing Decisions

- How and to what extent should information about pharmaceutical quality metrics be made available to external stakeholders?
- How might other stakeholders, such as buyers, use these metrics? What information would be most useful to them in making purchasing decisions?

Session Four: Opportunities and Challenges in Implementing a Core Set of Metrics

- What are the appropriate collection mechanisms for these metrics?
- How might quality metrics be collected by site or sponsor?
- What are the major challenges in defining these core metrics?
- What are the major process and technical challenges? (e.g., data and IT infrastructure barriers)?
- What are the major issues associated with 'gaming the system', and how might these be addressed?

Session Five: Presentation of a Metrics Discussion Set

DAY TWO

Session One: Exploring and Adapting the Metrics Discussion Set: Concerns, Additions, and Deletions

- What are the major concerns regarding the proposed metrics discussion set?
- What changes, addition, or deletions might be considered?

Session Two: Exploring and Adapting the Metrics Discussion Set: Definitions

- What are the major challenges in defining the metrics discussion set?
- Are there recommendations for changes, additions, deletions, or alternatives to these definitions?

Session Three: Exploring and Adapting the Metrics Discussion Set: Issues in Implementation

- What are the major issues in the collection of the data for the metrics discussion set?
- How might data for these metrics be collected? What mechanisms might the agency utilize?
- How frequently might these metrics be collected?
- Will these data be collected incrementally (e.g., quarterly) or at one standard interval?
- When might these data be collected? Will these data be collected according to the calendar year or based on a separate timeline?
- Are there challenges in collecting retrospective data from sponsors (e.g., collecting data from previous five years)?
- Will these data be collected from individual sites or sponsors at-large?
- What are the major challenges in the implementation of these metrics by the agency?

Session Four: Next Steps in Implementing the Metrics Discussion Set

- What questions and challenges still remain in the development and implementation of pharmaceutical quality metrics? How might these challenges be overcome?
- What are the main concerns of the stakeholders moving forward?