Advancing Product Quality: A Summary of the Second FDA/PQRI Conference

Meeting Report

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Introduction

The purpose of the Conference on Advancing Product Quality, under the sponsorship of the Food and Drug Administration (FDA) and Product Quality Research Institute (PQRI), is to bring regulators, industry professionals, and academic researchers together to create a synergized path toward enhanced global pharmaceutical quality. The 2015 FDA/PQRI Conference consisted of a plenary session and 20 breakout sessions arranged in four major tracks: (i) emerging regulatory initiatives; (ii) regulatory submission, assessment, and inspection; (iii) product and process development; and (iv) manufacturing, risk management, and quality assurance. This report provides a summary of the plenary session followed by each topic, as presented at the conference.

Progress and Challenges in Pharmaceutical Quality

The FDA regulates pharmaceutical drug products to ensure an uninterrupted supply of high-quality, safe, and effective drugs in the United States. The FDA's vision is to promote a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drugs without extensive regulatory oversight (1). Over the past decade we have seen significant progress toward this vision. However, at the same time, we have encountered new and increasingly complex challenges, which include unacceptable drug shortages, recalls, and threats to supply quality and reliability. The plenary session and related discussion covered the progress and challenges from regulatory, industry, and technology perspectives.

Regulatory Progress and Challenges

Since the 2014 FDA/PQRI inaugural Conference on Evolving Product Quality (2), the FDA has made significant progress in advancing product quality by:

- Formally documenting quality risk management in the quality assessment of abbreviated new drug applications (ANDAs), biological license applications (BLAs), and new drug

applications (NDAs);

- Developing and implementing team-based integrated quality assessment that incorporates review, inspection, policy, research, and surveillance;
- Publishing draft guidances (e.g., on quality metrics, established conditions, dissolution, BCS-based biowaivers, botanical drug development);
- Approving the first drug product utilizing a continuous manufacturing process, the first drug product utilizing 3D-printing, and the first biosimilar.
- Streamlining question-based review underpinning quality-by-design principles for both NDA and ANDA applications.

Of course, the most significant advancement was the formation of the Office of Pharmaceutical Quality (OPQ) in the FDA's Center for Drug Evaluation and Research. Standing up OPQ is a milestone in the FDA's efforts to assure that quality medicines are available to the American public (3). OPQ is organized to streamline regulatory processes, advance regulatory standards, align areas of expertise, and inaugurate the surveillance of drug quality. Supporting these objectives is an innovative and systematic approach to product quality knowledge management and informatics. Concerted strategies will bring parity to the oversight of innovator and generic drugs as well as domestic and international facilities. OPQ promotes and encourages the development and adoption of emerging pharmaceutical technologies to enhance pharmaceutical quality and reinvigorate the pharmaceutical manufacturing sector in the United States. This also applies abroad for drug product and API manufactured for the U.S. pharmaceutical market. With a motto of "One Quality Voice," OPQ embodies the closer integration and alignment of review, inspection, surveillance, policy, and research for the purpose of strengthening pharmaceutical quality on a global scale.

Industry Progress and Challenges

Two key dimensions to product quality are supply chain quality and reliability. A lack of drug safety and supply continuity are often attributable to quality issues. Solutions to resolve these

quality issues can be general or product-specific. The general solution focuses on improving quality risk management, pharmaceutical quality systems, and business processes. Product-specific solutions focus on processes, modalities, and platforms; as well as operational and technical/analytical considerations.

Quality does not happen in isolated “pockets,” rather it is built end-to-end and is continually challenged **(**as shown in Fig. 1**)**. Quality consists of four phases: plan, source, make, and deliver. The “plan” phase includes processes that balance aggregate demand and supply to develop a course of action that best meets sourcing, production, and delivery requirements. This phase is critical to meeting the needs of the target patient population. Despite the comprehensive nature of quality, the pharmaceutical industry may well need to design solutions by industry segment. For example, a one-size-fits-all model may increase risk of supply interruption in certain industry segments. Processes are needed to collaboratively predict demand and move to a model that incorporates replenishment based on true demand instead of forecast. Unfortunately, compared to other manufacturing industries, the pharmaceutical industry has generally poorly integrated demand into the plan phase (4).

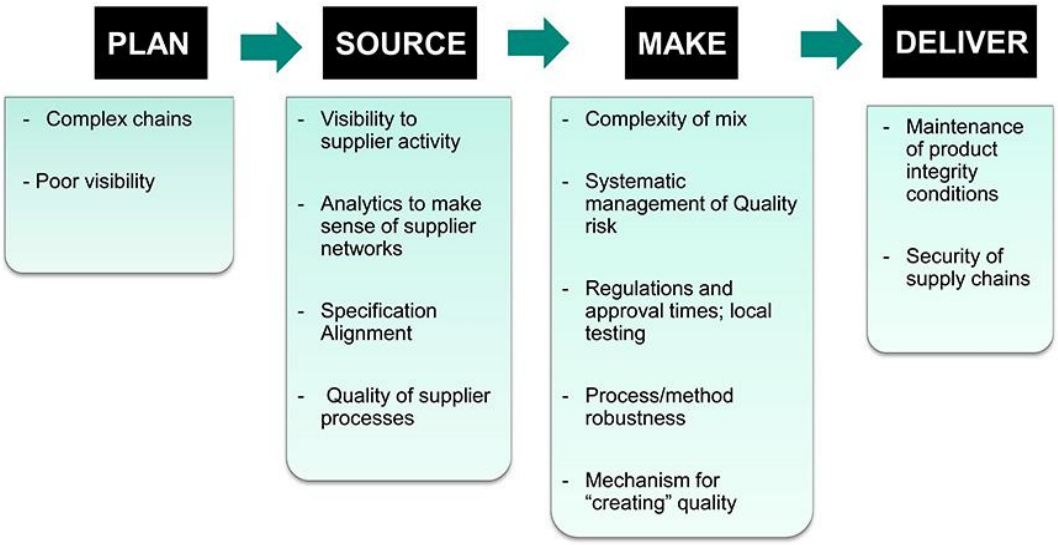

Figure 1. The Four Phases of Quality. Quality does not happen in "pockets." It is built end-to-end and it is continually challenged. Quality is about more than process and method. Holistic reliability is a critical part of quality.

The "source" phase includes processes that procure goods and services to meet planned or actual demand. The age of a US-centric, vertically integrated, life science industry has, for the most part, come to an end (5). In the past decade, sourcing and manufacturing has moved overseas in an effort to lower costs. With these changes, however, came increasing demand on pharmaceutical manufacturers to manage and control their supply chains, which are now longer and more complex. The pharmaceutical industry often fails to incorporate critical aspects of suppliers (i.e., original manufacturers, shippers, distributors, contract manufacturers, and suppliers) into their internal performance networks (e.g., specification alignment). The industry has insufficient knowledge of its suppliers with respect to quality and reliability, which often contributes to product recalls and drug shortages. The common practice is to conduct periodic audits of

suppliers, which is not sufficient. There is an urgent need to develop metrics to evaluate and monitor the quality and reliability of suppliers.

The “make” phase consists of processes that transform product to a finished state to meet planned or actual demand. A recent survey by Rita C. Peters from the biopharmaceutics industry has shown that Quality by Design (QbD) has improved process understanding (68.4%), improved product quality (66.7%), and reduced variability in product quality (57.9%) (4). Nearly half of the industry reported improved manufacturing efficiency as a result. However, almost 32% of the respondents had not implemented QbD. Reasons cited for not implementing QbD include a lack of guidance and direction from regulatory agencies (46.2%), no process or quality advantage to be gained (30.8%), a lack of understanding of the QbD initiative (23.2%), or the perception that it is too costly. Other factors include process robustness, quality risk management maturity, increased product complexity, and lack of international harmonization of regulations.

The “deliver” phase consists of processes that provide finished goods and services to meet planned or actual demand, typically including order management, transportation management, and distribution management. The challenges in this stage include supply chain security, product integrity in transition, and distribution information visibility.

Overall, the pharmaceutical industry needs to internalize the concept that “holistic reliability” (i.e., the ability of a supply chain to consistently deliver) is a critical part of quality. Quality is not just about process and method. It is also about visibility, information, predictability, and the systems to manage them. The ability to improve reliability comes both from systemic improvement and product-specific improvement. On the whole, the pharmaceutical industry’s challenges are not unique. Other manufacturing industries have addressed similar challenges and their successes can be leveraged.

Technology Progress and Challenges

Drug makers have used cutting-edge science to discover medicines, but they have manufactured them using techniques dating to the days of the steam engine (6). Pharmaceutical manufacturing processes are falling behind other industries in terms of technology and efficiency. Now, the industry is moving toward a major upgrade from batch to continuous production (7) (see also Fig. 2). Under the new approach, raw materials are fed into a single, continuously running process. Many other industries adopted such a continuous approach years ago, because quality can be checked without interrupting production. This leads to weeks shaved off production times and significant cuts in operating expenses. Until recently, pharmaceutical companies have manufactured drugs the old-fashioned way, mixing ingredients in large vats and in separate steps, often at separate plants, with no way to assess quality until each step is finished.

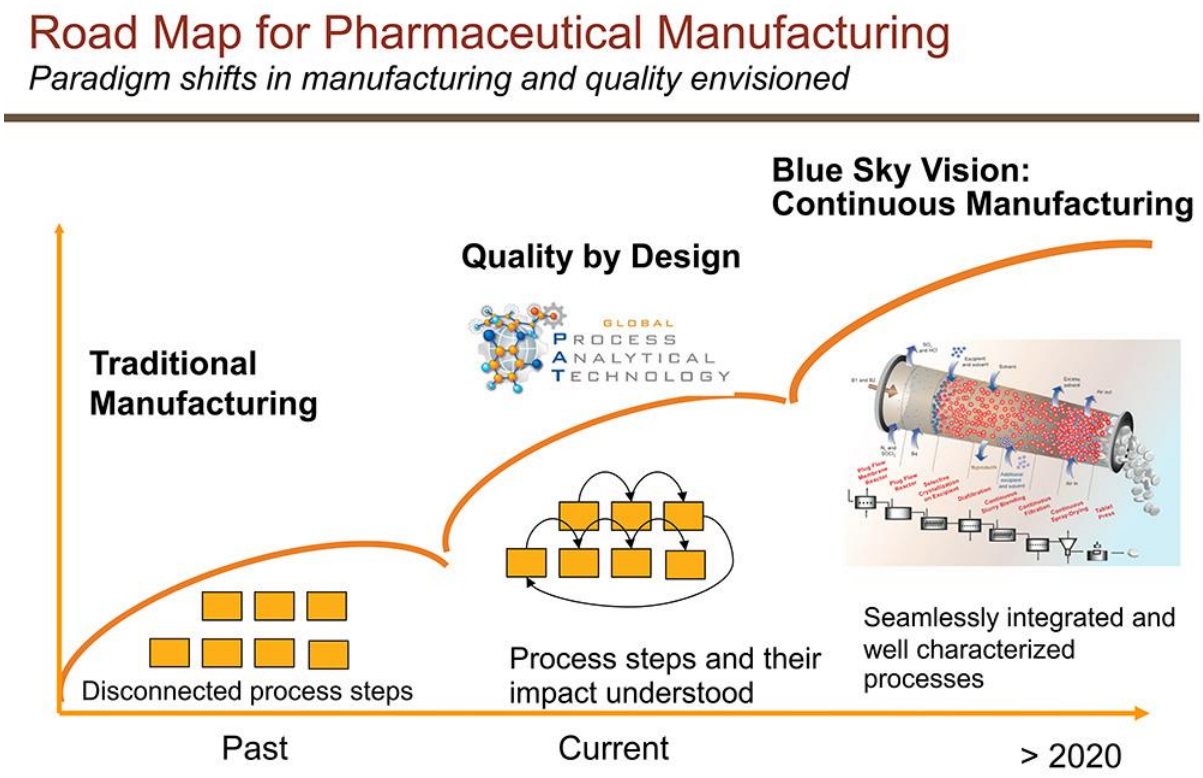

Figure 2. Road Map for Pharmaceutical Manufacturing. Over the last decade there has been a paradigm

shift in pharmaceutical manufacturing, moving away from fixed processes, where product quality is confirmed solely though end-product testing, to the Quality by Design paradigm (QbD). QbD is a systematic scientific and risk-based approach to pharmaceutical manufacturing where quality is built-in through product and process understanding. Continuous manufacturing represents the next paradigm shift and provides an opportunity, through integration and the application of systems-based approaches, to adopt advanced manufacturing process development and control systems to produce high quality products. This reduces waste resulting from the generation of out-of-specification material. Since in its ultimate manifestation a continuous process is designed as a whole, the distinction between the drug substance process and the drug product process can potentially be eliminated. This blue sky vision can be achieved through the adoption of novel process technologies.

The significant benefit of a continuous process is the integration of chemical operation and formulation into one solution, allowing a constant, fully automated process in which raw materials are introduced at one end and products come out the other. The FDA, once viewed as a potential obstacle to manufacturing innovation, is actively promoting and supporting moves to continuous processes. The FDA, seeing an opportunity to improve the overall quality and reliability of drug manufacturing, began pushing for such change in 2004 (1). Indeed, in 2015 the FDA approved the first new drug application that contains a continuous manufacturing process (8).

During the plenary session, Bernhardt Trout presented the first example of an end-to-end, integrated continuous manufacturing plant for a pharmaceutical product from his group at MIT (9). It starts from a chemical intermediate and performs all intermediate reactions, separations, crystallizations, drying, and formulation, which results in a formed final tablet in one tightly controlled process. This plant provides a platform to test newly developed continuous technologies within the context of a fully integrated production system. In addition, this plant provides a means to investigate the system-wide performance of multiple interconnected units.

In summary, significant progress has been made by regulators, industry, and academia to support and advance product quality. With the creation of OPQ, the acceptance of QbD by industry, and the technological advancements in continuous manufacturing processes, the stage is set to deliver pharmaceuticals of unprecedented quality to the American public. If quality is promoted,

designed, and built appropriately, this will be a truly rewarding endeavor that has the potential to benefit the industry and the patient.

Emerging Regulatory Initiatives

Biopharmaceutics Classification System (BCS) Biowaivers

In August 2000, FDA issued a guidance for industry on waiver of *in vivo* bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on BCS (10). The BCS is a scientific and risk-based framework for classifying a drug substance based on its aqueous solubility and intestinal permeability (11). When combined with the *in vitro* dissolution characteristics of the drug product, the BCS takes into account three major factors that govern the rate and extent of oral drug absorption from IR solid oral dosage forms: solubility, intestinal permeability, and dissolution rate. In 2002, the FDA issued a guidance recommending that food effect bioequivalence studies were not needed for BCS Class I drugs dosed in immediate release forms that exhibit rapid dissolution (12). To ensure accuracy and consistency, the FDA formed the BCS Committee who has the responsibility and authority to make the determination of BCS classification of new or generic drugs. The committee has classified a total of 42 drugs as BCS Class I drugs (i.e., rapidly dissolving, immediate-release drug products containing high solubility and highly permeability drug substances). The determination not only helps to ensure the availability of new or generic drugs, but also saves sponsors hundreds of millions dollars of clinical studies. Further, the FDA recently released a draft guidance extending the biowaiver to BCS Class III drugs (i.e., very rapidly dissolving, immediate-release drug products containing high solubility but low permeability drug substances), which will further accelerate the development of drugs and reduce the amount of costly *in vivo* studies (13). A point highlighted at the conference is that future efforts in this arena should focus on global harmonization of classification systems for biowaivers.

Pharmaceutical Product Lifecycle Management – Q12

There are a number of challenges faced by industry and the FDA (as well as other regulatory authorities) when it comes to managing post-approval changes. These challenges have a direct impact on lifecycle management and may lead to: (i) lack of proactive implementation of manufacturing (and other) improvements; (ii) inefficient use of industry and regulatory resources; (iii) not fully realizing the benefits and operational flexibility expected by the implementation of ICH Q8 – Q11; and (iv) supply chain disruption and potential drug shortages.

In 2014, at the ICH Quality Strategy Workshop in Minneapolis, workshop participants reflected on the progress since publication of ICH Q8 – Q11 (14). They proposed a 5-year strategic plan including the development of a vision and strategy for pharmaceutical product lifecycle management. At the ICH 2014 workshop, the ICH Steering Committee endorsed the proposal to establish an Expert Working Group (EWG) to develop a new guideline, "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management – ICH Q12." ICH Q12 is a priority for industry and regulators and is intended to bring more focus on the commercial manufacturing phase of the lifecycle, while bridging the development phases that were already covered in the aforementioned guidelines. ICH Q12, as noted in the concept paper (15), is unique to ICH "Q" guidelines as it is intended to tackle not only technical challenges in managing a product's lifecycle, but also regulatory challenges. These regulatory challenges include some complex regulatory processes that are not always science- and risk-based. These challenges include clarity on what constitutes regulatory commitments or established conditions (16) and their relationships to controls (as shown in Fig. 3)**,** best practices for change and knowledge management as lifecycle management enablers, as well as exploring opportunities to harmonize global data requirements to support post-approval changes.

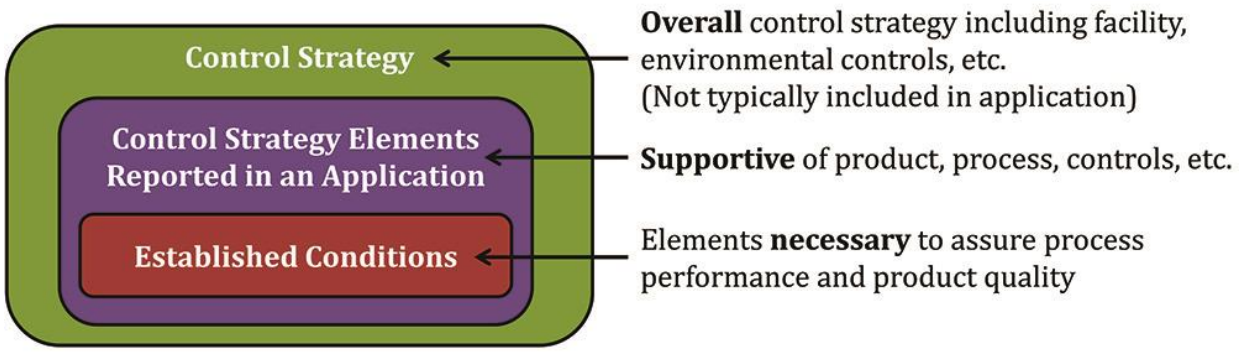

Figure 3. Established conditions and their relationships to controls. Established conditions are part of an overall control strategy and are essential to assuring product quality. Established conditions are included in the elements of the control strategy reported in an application.

At this critical stage in the drafting of the ICH Q12 guideline, feedback received at the conference informs the Q12 EWG on several themes critical to realizing the vision of the guideline. These themes include: (i) exploring how to provide FDA (and other regulators) confidence in the reliability of industry's change management systems; (ii) better utilizing regulatory tools, (e.g., a robust Pharmaceutical Quality System (PQS), New Inspection Protocols Project (NIPP), records requests in lieu or in advance of inspection, and enhanced knowledge management); (iii) tying the level of detail and change management of established conditions to risk and level of product and process knowledge; and (iv) providing a clear pathway for legacy and generic products to realize the opportunities and benefits of Q12.

Dissolution Testing

"What is currently impossible to do in my field but, if possible, would fundamentally change it?" posited the futurist Joel Barker (17). For an important segment of the pharmaceutical field focused on solid oral dosage forms, the answer is a better, more predictive dissolution test. Dissolution is one of the most important quality attributes of a solid oral drug product. Dissolution testing serves as a critical tool to ensure consistent quality and performance of both development and commercial products. It is also critical for the evaluation of relative product performance resulting from changes in formulation and/or manufacturing processes. Prior to regulatory filing, it guides formulation and process development and facilitates assessment of critical process parameters, design space, risks, and development of appropriate control strategies. Post-approval, it assures batch-to-batch consistency of product and supports proposed changes in formulation and manufacturing processes. The major problems with current dissolution methodologies are that they may be over- or under-discriminating or, at worst, completely irrelevant to *in vivo* performance.

Standard compendial tests for "oral bioperformance" include the disintegration test adopted in the 1950s, the dissolution apparatus 1 (basket) adopted in 1970, and the dissolution apparatus 2 (paddle) adopted in the 1980s (18). Since then, little advancement has occurred in the field of dissolution testing despite the breakthrough in modeling and simulation of oral drug absorption. Future dissolution testing may well need to transition to multiple dissolution methodologies for different purposes (e.g., fit-for-purpose dissolution methodologies). For quality control purposes, the dissolution test needs to be simple, fast, and affordable. However, the dissolution test also needs to reflect the situation *in vivo*. A variety of non-compendial dissolution methodologies are currently being evaluated and used in academia, industry, and regulatory agencies in pursuit of test methods that more accurately represent what is now known of human gastrointestinal physiology (19). The goal is better assessment of *in vivo* performance.

The FDA is keenly interested in modifying dissolution testing to be more clinically relevant. As a first step, the FDA recently issued a draft guidance on dissolution testing and specification criteria for immediate-release solid oral dosage forms containing BCS Class 1 and 3 drugs (20). For drug products of these classes, the guidance recommends standard test conditions (i.e., 100 RPM Basket USP apparatus 1 or 75 RPM Paddle USP apparatus 2), dissolution media (i.e., 500 mL of 0.01M HCl with no surfactant at 37 ^{o}C), and acceptance criteria (i.e., Q = 80% in 30 minutes for BCS Class 1 and in 15 minutes for BCS Class 3). The scientific rationales for this guidance are that: (i) the low risk of patient-relevant dissolution failure, (ii) the more physiologically relevant media and volume, and (ii) the need to meet the dissolution criteria, will likely yield *in vivo* equivalence.

Investigating *in vitro* methods generally has one goal: getting the "optimal" *in vivo* release rate and then maintaining the desired performance over the life of the product. There is much on-going research within industry to advance *in vitro* methods predictive of *in vivo* outcomes and to develop clinically relevant specifications for extended release products. Example research includes: (i) the use of osmotic systems to rapidly assess *in vivo* viability and confirm biopharmaceutical models; (ii) coupling biopharmaceutics models with digital dosage form design to select extended release formulation composition; (iii) radio labelling and scintigraphy to identify lead formulations and obtain useful *in vivo* information; and (iv) conducting chemical analysis to assess matrix effects on dissolution. Remaining challenges include addressing disintegration throughout the gastrointestinal track. However, the effects of such disintegration are still not clear. Depending on the matrix and nature of the drug, other aspects, such as diffusion may be of more importance. The conference made clear the united viewpoint that, whenever possible, *in vitro* quality attributes need to link to *in vivo* performance to minimize risks to patients and assure consistent oral bioperformance.

Quality Metrics

Quality metrics are expected to play an important role in achieving the desired state of pharmaceutical quality. Quality metrics programs are used throughout the pharmaceutical

industry to monitor quality control systems and processes and drive continuous improvement efforts in drug manufacturing. Since 2013, the FDA has been discussing with stakeholders how to select a subset of ideal metrics that are mutually useful and objective. The FDA is committed to supporting the modernization of pharmaceutical manufacturing and expects that this program, along with other surveillance programs, will encourage improved behavior and responsibility in this area by identifying and rewarding establishments that go "above and beyond" the minimum quality standards.

The FDA published a draft guidance on quality metrics in July 2015 (21). This guidance recommends four metrics: (i) lot acceptance rate, (ii) product quality complaint rate, (iii) invalidated Out-of-Specification rate, and (iv) annual product review or product quality review on time rate. Optional metrics include senior management engagement, corrective action and preventive action effectiveness, and process capability/performance (see discussion of process capability below under Manufacturing and Quality Assurance). The FDA intends to use the information in order to provide more insight into the state of quality for product and facility; provide more quantitative and objective measures of quality at the product, site and system levels; enhance the risk-based surveillance inspection scheduling model; improve effectiveness of inspections; and help identify factors leading to supply disruption. Further, this information may provide a basis to assist in determining the appropriate reporting category for post-approval manufacturing changes. Multiple international pharmaceutical manufacturers have submitted positive comments to the docket endorsing a mandatory program. Two medical gas associations have even suggested the scope be expanded to include their products. Others, however, have expressed concern with the enforcement tone of the draft guidance.

Representatives from both industry and the International Society of Pharmaceutical Engineering (ISPE) are supportive of FDA's effort in addressing quality metrics while recognizing that standardization across industry is difficult. ISPE recommendations start with three of the FDA's proposed metrics: (i) lot Acceptance Rate (reported by site, differentiated by product), (ii) product quality complaints (reported by product only), and (iii) invalidated Out-of-Specification

rate (reported by site, differentiated by product). ISPE recommends deferring annual product review or product quality review on time rate. ISPE recommends reporting by site, differentiated by product since it is more representative of how industry currently gathers quality data and therefore may reduce the burden for startup of the program.

All of the conference presenters in this session agreed that the context of each data point and metric matters and a single metric cannot independently be used to judge quality. Additional areas of discussion included: (i) calculating the product complaint rate by units and not by lot; (ii) corrective action and preventive action effectiveness/retraining rate; (iii) the annual product review on time rate; (iv) supply chain visibility (e.g., contract manufacturing being part of reporting); and (v) non-application product complexities (e.g., national drug code numbers may not be differentiated until final packaging, challenging upstream metric reporting at this detail in over-the-counter industry). Ultimately, quality metrics programs will improve patient access to important therapies by increasing the quality and reliability of drug supplies.

Botanical Drug Development and Quality Standards

There is a renewed interest in the discovery of novel therapeutic molecules from botanical sources, especially after Dr. Youyou Tu was awarded the Nobel Prize in Physiology or Medicine in 2015 for her contribution to the initial discovery of artemisinin and its use in the treatment of malaria (22). In contrast to artemisinin, which is highly purified, botanical drug products generally consist of naturally-derived complex mixtures of vegetable materials, which may include plant materials, algae, macroscopic fungi, or combinations thereof. These mixtures contain many different chemical components and exhibit considerable variability (e.g., in phytochemical profile) that is inherent from natural variations at the organism level. Due to the uncertainty of the active component(s) in a botanical mixture, the FDA generally considers the entire mixture as the active ingredient for botanical drugs derived from a single botanical raw material. New botanicals intended to be marketed as drugs in the United States are expected to meet the same standards as non-botanical drugs for quality, safety, and efficacy. As a result,

while botanicals could be an important source for new drugs, their development remains a great challenge due to their inherent complexity. Therefore, they have not been in the mainstream development of the pharmaceutical industry.

To facilitate the development and regulatory evaluation of botanical drugs in the United States, the FDA published its first guidance on Botanical Drug Products in 2004 (23), and issued a revised draft guidance on Botanical Drug Development in 2015 (24). The 2015 draft guidance provides recommendations on quality, nonclinical, clinical, and other unique aspects associated with botanical new drug development through the investigational new drug (IND) and new drug application (NDA) processes. Most importantly the draft guidance describes the "totality-of-evidence" approach for quality control of botanical drugs that overcomes the limited ability to characterize the entire botanical mixture or its active components by analytical means. In addition to conventional CMC data, this integrated approach considers other evidence including raw material control, clinically relevant bioassay(s), and other non-CMC data. The degree of reliance on these other data for ensuring consistency of quality depends on the extent to which the botanical mixture can be characterized and quantified. Using this approach, the FDA approved the first botanical NDA for Veregen (sinecatechins) in 2006, and the second botanical NDA for Fulyzaq (crofelemer) in 2012. These two NDA approvals show that new therapies derived from natural complex mixtures can be developed to meet modern FDA standards of quality, safety, and efficacy.

Despite the approval of two botanical products under the NDA pathway, more research is still needed to address challenges related to the characterization and quality control of botanical raw materials, drug substances, and drug products. For botanical raw materials, fast, simple, and fit-for-purpose screening methods should be developed for accurate plant species identification. There is also a need for cataloging possible environmental contaminates (e.g., pesticides and heavy metals) related to the plant source. For drug substances and products, analytical methods should be improved to better characterize the heterogeneity and variability of botanical mixtures in relation to harvesting techniques and/or manufacturing conditions

(e.g., extraction). A better scientific approach should also be developed to assess drug substance stability and understand its impact on botanical drug quality, safety and efficacy. This will require collaborative efforts among the industry, academia, and government agencies.

Regulatory Submission, Assessment, and Inspection

Breakthrough Therapy – CMC Challenges

The FDA Safety and Innovation Act (2012) Section 901 and 902 introduced fast track and breakthrough therapy designations. Breakthrough therapy designation is for serious and life-threatening conditions and granted based on preliminary clinical evidence using a risk-based approach (e.g., obtained during Phase 1 or Phase 2). For Breakthrough drugs, the FDA allows reduced research, development, manufacturing, and processing timelines while not reducing CMC quality expectations. As such, several flexible approaches are employed during the review process including rolling submissions, supplements, postmarket requirements, and postmarket commitments. For example, agreements have been reached on submitting less stability data at initial application with submission of data as it becomes available.

Accelerated filing and review is challenging for both FDA and industry. For FDA, there are: (i) less available CMC data (e.g., safety, stability, processing, manufacturing); (ii) additional amendments during the application lifecycle; (iii) needs for earlier identification and inspection of facilities; (iv) increased treatment protocols/expanded access submissions; and (v) increased postmarket requirements and postmarket commitments to cover residual risk. For industry, it requires: (i) high clinical demands; (ii) detailed product lifecycle planning; (iii) pre-approval inspection readiness; (iv) establishment of meaningful specifications; and (v) development of robust manufacturing processes. The key to mitigating risks and solving unexpected issues is early, open, and increased communications between the sponsor and the FDA. Sponsors have found that timely and meaningful communications with the FDA are essential when issues arise. When working collaboratively, FDA and sponsors are able to explore, troubleshoot, and resolve

unexpected issues throughout the lifecycle of breakthrough drugs. At the conference it was evident that industry is hoping to establish clear, consistent, predictable, and transparent policies and processes. These should be developed with stakeholder input that aligns pharmaceutical development and commercial manufacturing programs to applicable regulatory pathways.

Pre-Approval and Surveillance Inspection

FDA conducts inspections of manufacturing operations for two primary reasons: (i) to evaluate a manufacturing operation before granting approval and (ii) to verify, through periodic evaluation of all manufacturing facilities, that manufacturing is in a state of control. To this end, a pre-approval inspection (PAI) may be performed. The PAI, as its name implies, is part of the application review process to evaluate: (i) site readiness for commercial manufacturing, (ii) conformance to the marketing application, and (iii) data generated at the site for authenticity, reliability and accuracy. The decision to conduct a PAI depends on facility, process, and product risks.

The PAI inspection can give FDA valuable information and assurance on behalf of patients that any new drug will be manufactured in a manner that assures its demonstrated safety and efficacy. A PAI can: (i) more efficiently and effectively resolve certain review issues identified during the application's off-site review, (ii) improve the reviewers' understanding of the process and product, and (iii) enable substantive discussions about the process and control strategy (including any PAT-based monitoring, model maintenance and decision trees). A PAI also provides FDA experts with an opportunity to more fully assess information not contained within the standard application that relates to general facility issues. In particular this includes how the proposed new drug will be incorporated in an existing non-dedicated facility, including discussions on trending, continued process verification, and risk management. The FDA may also inspect a facility after granting approval and soon after distribution to verify that the commercial-scale manufacturing operation, including control strategy, results in the drug as it

was designed and approved. The most significant discussions at the conference regarding PAIs resulted the recommendations that: (i) application reviewers from different disciplines participate in inspections more often, (ii) the same inspection team perform inspections of all manufacturing facilities cited in the application, (iii) the FDA increase its coordination with other regulators performing facility inspections, (iv) the FDA not issue a written notice of observations (FDA 483) at the end of a PAI, and (iv) the FDA submit questions in advance of a facility inspection.

A surveillance inspection is performed to verify that drugs, both active ingredients and finished products, are manufactured according to the FDA's regulations governing minimum quality standards (i.e., current good manufacturing practices). Surveillance inspections also provide industry an opportunity to learn from the observations, assess whether current practices align with recommendations in FDA guidance, and provide the FDA with current information on industry practices. Current surveillance inspections focus on CGMP violations and generally result in a determination of the need for further regulatory action (e.g., warning, seizure, import alert, injunction). A possible different approach discussed at the conference would be determining a facility's overall quality capability along a scale (low to high) to provide for suitable regulatory intervention at lower functioning facilities and reduced regulatory activities at higher functioning facilities.

The ideal surveillance inspection to assure product quality might better recognize and encourage the two fundamental elements of good quality management, which are that: (i) risk is systematically understood and mitigated and (ii) risk management and efforts to assure robust drug quality are promoted and incentivized. This would require a holistic and collaborative approach between industry and regulators. The concerns with current surveillance inspection include: (i) the lack of apparent incentives for the proactive enhancement of manufacturing quality, (ii) limited use of risk-based approaches by regulators resulting in inefficient use of industry (and regulatory) resources, (iii) inconsistencies in regulatory inspections (and other review and enforcement disciplines), and (iv) a lack of

harmonization among regulatory agencies. Recommendations for future approaches include: (i) incentivizing high-functioning manufacturing operations, (ii) developing a shared quality problem reporting system adapted from the aviation safety reporting system, and (iii) considering certain standards for quality such as in the seafood hazard analysis critical control point program. The FDA is developing a more structured and question-based inspection program supporting a more objective categorization of each facility's quality management system (i.e., "new inspection protocol project").

Risk-Based Regulatory Approach

The desired state of the risk-based regulatory approach involves open communication between the industry and FDA. Beyond open communication on an ongoing basis, applications provide additional transparency regarding risk uncertainty as well as design, development, and robustness of the quality control strategy for a particular product. In the spirit of transparency, industry should be open to sharing risk assessments or their approach to risk assessment with the FDA, but this openness should not be penalized. In addition, both the industry's and the FDA's focus should be on risk and quality, not merely compliance.

The current state of the risk-based approach for ensuring product quality is far from perfect. There are an unacceptable number of product recalls and drug shortages and there is not enough transparency from industry or regulators. The FDA would like to know how the industry performs risk assessments. Meanwhile the industry is concerned with inconsistencies in regulatory assessments/inspections and global divergence. Better understanding of product quality and control strategies will increase FDA confidence in the industry's ability to manage quality.

Barriers to transform from the current to the future state include: (i) cultural inertia; insufficient incentives; (ii) lack of standardization of tools, techniques, systems for risk assessment; (iii) lack of trust between the industry and regulators; (iv) lack of open

communication and mutual recognition; (v) lack of lifecycle focus; and (iv) cumbersome submission formats. The short-term goal is to improve transparency on both sides by: (i) providing clear expectations to industry, (ii) ensuring appropriate control strategies are in place, (iii) distinguishing risk from characterizing uncertainty, (iv) sharing risk assessment techniques to improve the FDA's confidence in data, and (v) determining and confirming predictability of risk assessment techniques. The long term goal is to build a collaborative relationship between industry and the FDA. Transparency from both sides will increase confidence and trust, and standardize risk assessments. However, both sides need to have the same intentions (e.g., operations, vision, creativity, quality standards). Both sides should focus on patient safety and work together to create robust assessment tools and systems.

Quality Risk Management

Risk management drives the focus of Quality Management Systems (QMSs), helps define level of effort of those activities, and supports risk-based decisions of quality management. Integration of risk management into QMSs can help to drive efficiency and effectiveness and reduce injury rate, backlog, inventory, capital, and losses (as shown in Figure 4). A QMS includes development, evaluation of quality defects, auditing and inspection, periodic product reviews, and change control.

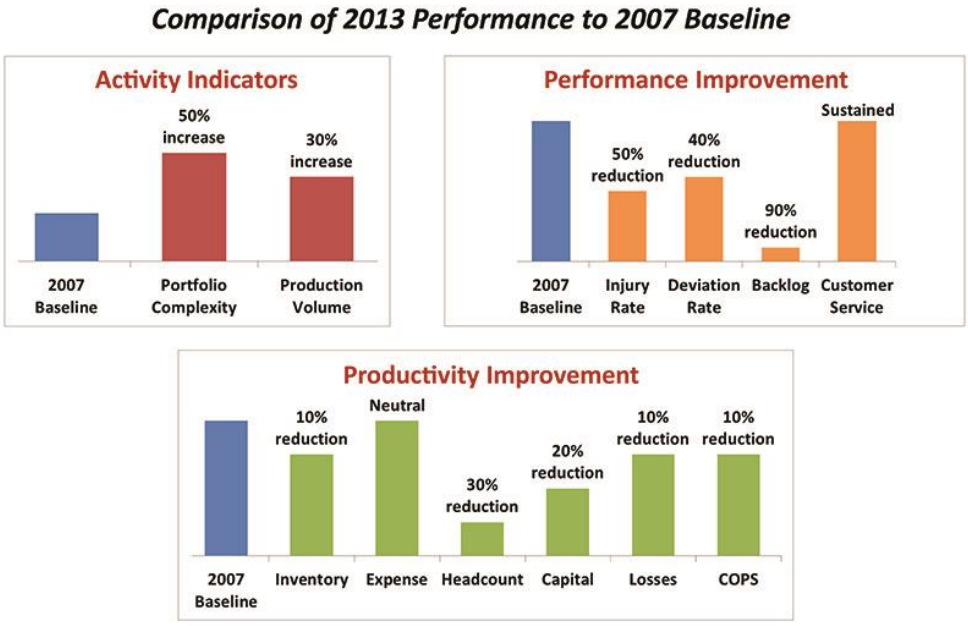

Figure 4. Quality risk management and process capability. By focusing on integrating quality risk management into quality management systems and pursuing process capability, Lilly has delivered improvements including reductions to the injury rate by 50% and to the deviation rate by 40% from 2007 to 2013.

Quality risk management (QRM) is used to guide development of a robust control strategy that ensures critical quality attributes are established and attained (i.e., risk assessment). The capability of the process and robustness of the control strategy to reproducibly deliver quality product should be evaluated periodically to ensure continued suitability (i.e., risk review). Risk management is incorporated into manufacturing governance by:

- Orthogonal reviews of product, site, and system to obtain comprehensive assessment of risks and maintain a risk file;
- Updates based on production (e.g., nonconformities, process changes, supplier changes), market (e.g., complaints, adverse events, customer inquiries), and changes in industry and regulation (e.g., new requirements, information on similar marketed

products);

- Planning activities for the long-term (e.g., business strategy, policy, portfolio, enterprise goals), mid-term (e.g., operational strategy, key objectives, global governance, performance targets) and short-term (e.g., resource deployment, shop floor execution, process control, monitoring);
- Management involvement, escalation, decision making, and auditing.

The QRM scope should include worst-case situations prospectively, resulting in the generation of knowledge to understand risks and/or implement controls to mitigate risks. In particular, leadership should: (i) focus on risks associated with human behavior; (ii) fully understand the perspective of individuals manufacturing the product; and (iii) implement appropriate levels of authority, incentives, and controls to mitigate quality issues.

The importance of QRM in remediation of compliance issues after regulatory actions have occurred is paramount. QRM should be integrated across systems to ensure orthogonal reviews of the entire manufacturing process (e.g., setup every site the same to maintain the level of quality control). This integration should reduce confusion and streamline the functionality of QMS using common quality practices. QRM can be aided by continuing to improve quality control strategies based on common deficiencies and creating global standards to have more accountability throughout the process. It is clear that governance is very important to the success of QRM.

FDA Integrated Quality Assessment

OPQ has developed and implemented a team-based Integrated Quality Assessment (IQA). This approach maximizes each team member's expertise and provides aligned patient-focused and risk-based drug product quality recommendations, inclusive of drug substance, drug product, manufacturing process, and facilities (as shown in Fig. 5). An IQA team is designed to work in a highly collaborative model within PDUFA/GDUFA timelines. Reviewers in the IQA team focus on

quality risks as they relate to patient needs and communicate information requests or deficiencies in terms of mitigating risks to clinical performance. The review is done with the consideration of clinical and regulatory frameworks with lifecycle approaches. Open communication and dialogues of quality risk and link to the patient are critical to the success of the IQA approach.

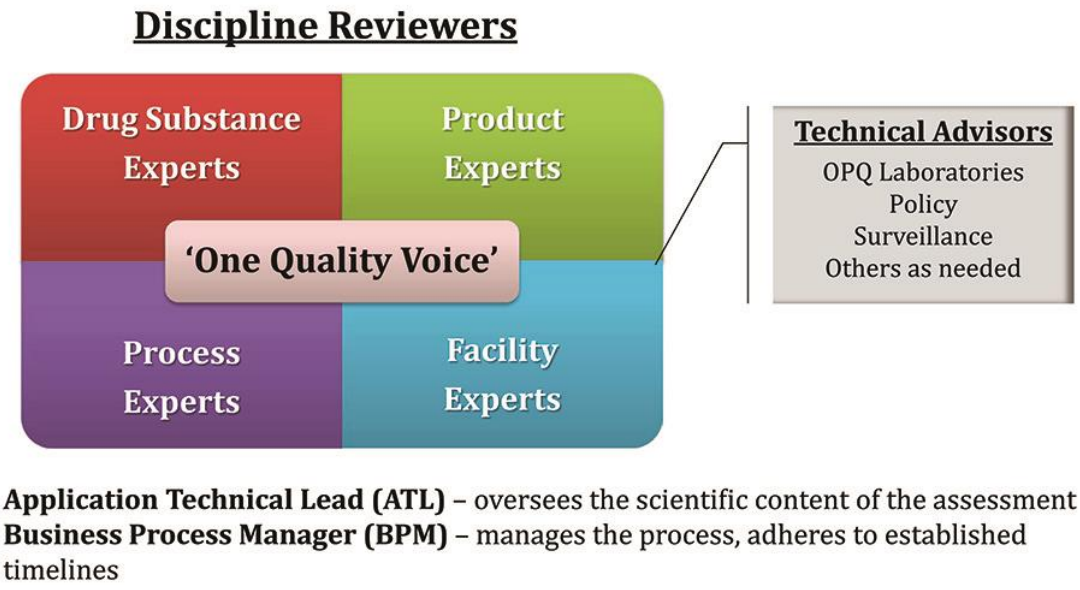

Figure 5. FDA team-based integrated quality assessment. Team-based integrated quality assessment consists of discipline reviewers of drug substance, drug product, process, and facility. Formal risk assessment is used to enhance efficiency and effectiveness of review and inspection. Integration of review with inspection produces more informed decisions on facility acceptability and application approvability.

The team-based IQA approach emerged from both new and generic drug reviews. For new drugs, it evolved from the QbD pilot and team-based reviews on breakthrough submissions. For generic drugs, it progressed from the integration of drug substance/drug product pilot in 2010. It advanced as part of OPQ reorganization and GDUFA implementation along with the use of real-time communication. All new and generic applications as well as CDER-managed biologics

license applications (BLAs) submitted after October 1, 2014 have been reviewed using the IQA approach. In fact, the recent approvals of the continuous manufacturing drug product and 3D-printed drug product applications are outcomes of the IQA approach (8, 25).

The purpose and benefit of the FDA IQA are clearly understood and supported by the industry. Reviews of approved NDAs from 2011 to 2015 revealed that common areas for deficiencies were process control and specifications (together 60% of deficiencies). As a result of implementation of IQA, consistent drug product quality assessments have been observed. There exists improved alignment in areas such as criticality, process description and control strategy. Still, there are opportunities for further dialogue. Industry participants noted that information requests should be considered deficiencies in information provided in a submission, not necessarily a deficiency in a firm's development program. For ANDAs, there has been an observed increase in total number and diversity of questions (i.e., questions have apparently been generated by a team, compared to the more focused questions of the single-reviewer approach). These questions are fundamental in nature with respect to both product and process understanding. ANDA sponsors have observed very high expectations for mitigation strategy on all risks. Implementation of QbD principles is needed for all ANDAs.

FDA and industry are aligned in drug product quality on behalf of the patient. More effective, transparent, and risk-based communication linking quality to clinical performance is expected. Further discussion is needed on making quality management system information transparent to regulators to build trust, and on managing blurred lines between reviewers and inspectors. At the conference suggested improvements to the IQA process included:

- FDA communication through IRs/deficiencies should make clear the rationale behind the question.
- Application team leads should have a stronger role in consolidating questions and ensuring applications are properly supported.
- Keeping and expanding on the dialogue between FDA and industry. Can FDA provide best practices and/or expectations for risk assessments (e.g., how much information

to provide and where to provide it)?

- A potential for a face-to-face meeting shortly after starting submission review for NDAs.
- Encouraging industry to ask for clarity regarding questions that are unclear, appear unsupported, or might generate an unexpectedly voluminous response.

Product and Process Development

Characterization of Complex Drug Formulations Containing Nanomaterials

FDA is receiving and approving an increasing number of applications for complex drug formulations containing nanomaterials. These products are regulated and reviewed in the same manner as drug products not containing nanomaterials. Challenges to both industry and regulators alike for the development and regulation of these products often stem from ensuring appropriate and adequate characterization in order to maintain product quality. In particular, determining which methods will be used for characterization is a subject of much debate.

Although critical quality attributes for any product are ultimately product-specific, size distribution is a much-cited attribute for the characterization and control of nanomaterials. The size distribution of different formulations containing nanoscale materials has been demonstrated to impact product performance and is thus often measured during product development, as well as in release and stability specifications. Dynamic light scattering (DLS) is the most common sizing technique seen by both industry and FDA. However, for determining size distributions, this technique must be supplemented with another complementary method to adequately characterize the size distribution of the nanoscale materials. The FDA and industry agree that a comprehensive particle size control strategy is essential for products containing nanoscale materials.

Size is not the only critical quality attribute for drug products containing nanomaterials. Other attributes (including non-nanoscale attributes) such as morphology, drug release, and surface charge often impact product performance. The determination of the critical quality attributes will ultimately be product-specific and discussions between the industry and FDA are recommended to clarify critical quality attributes and their measurement in order to accelerate the development and approval of these complex formulations.

Biosimilar Product Assessment – How Similar is Similar?

The Biologics Price Competition and Innovation Act, a part of the Patient Protection and Affordable Care Act signed into law on March 23, 2010, amended the PHS Act by creating a licensure pathway for biological products demonstrated to be biosimilar to, or also interchangeable with, an FDA-licensed biological reference product. The FDA issued a series of guidance documents to aid the development of biosimilar products. On March 6, 2015 FDA approved the first biosimilar product, Sandoz's Zarxio, biosimilar to Amgen's Neupogen (26). Nevertheless, challenges in the development of biosimilar products were presented and discussed by FDA and industry representatives.

Development of the product is a continuum, thus, analytical similarity should be evaluated at every stage (e.g., pre-IND, IND-enabling, pharmacokinetic/pharmacodynamic studies, supporting licensure). Multiple reference lots, in some examples 20-30 lots, were used, spanning a period of 4-5 years. Lots that are used in pivotal clinical studies should be part of the analytical similarity assessment. Issues that arise during product development may relate to potential shifts in quality attributes of the reference product. Therefore, if the shift occurs during early development of the biosimilar, it is possible to integrate the new lots in the development program and adjust the process to match the quality attributes of the reference product. For a mature program, the industry perspective was that the biosimilar should maintain the original target profile. The recommendation was to engage the FDA in discussion as such issues arise. Another potential issue is the analytical drift that can be introduced by instrument or personnel changes. This drift is

mitigated by use of reference standard and appropriate assay suitability criteria, highlighting the importance of consistent reference standard materials and of a two-tier reference standard system.

The use of statistical tools to evaluate analytical similarity was another discussion topic at the conference. The FDA goal is to make the program successful and inspire confidence in the public and health care provider communities. Industry representatives highlighted some of the challenges. The number of lots used in the analytical similarity assessment is important, as a small number of lots may not be sufficient to capture the variability of the product. The FDA recommends a statistical approach based on risk ranking of quality attributes, with risk levels linked to statistical tiers (i.e., Tier 1 - equivalence testing, Tier 2 - quality ranges, and Tier 3 - visual comparison). Not all highly critical quality attributes will be assigned to Tier 1. The risk assessment is product specific, as is the assignment of attributes to be specific statistical tiers. In terms of equivalence testing, it is difficult for industry to target manufacturing ranges when the equivalence margins are very tight. In conclusion, there is a need for FDA guidance on statistical evaluation of analytical similarity.

Palatability and Swallowability

Patient acceptance of the drug product and adherence to the prescribed therapy are critical for achieving the intended therapeutic benefit. The mouthfeel is a critical quality attribute for oral drug products and includes a spectrum of assessments such as texture, taste, smell, palatability, and swallowability. Mouthfeel is especially important in pediatric populations where patient acceptance of the dosage form may be more difficult to achieve as compared to adults. Mouthfeel assessments can be performed in taste panels (e.g., sensory methods in adults and pediatric patients) and also performed *in vitro* using specific tools and techniques.

The session highlighted the possibility of learning and leveraging opportunities from the methods applied for describing and improving mouthfeel of foods. It focused on tribology which captures

processes that contribute to mouthfeel and the use of electronic sensors (e.g., electronic tongue) in formulation development for palatability and taste-masking. Since the 1960s, a significant body of knowledge, expertise, and techniques continue to be developed for understanding consumers' perception of mouthfeel of foods and beverages. This knowledge has been used for designing and optimizing foods (including liquids) that are acceptable to consumers. The fundamental measures (e.g., hardness, viscosity, elasticity, and shear stress) used in foods for quantifying and translating into consumer experience (27) are also measured in pharmaceutics for assessing drug product attributes.

In food engineering, tribology helps to understand the oral processing of food as well as texture and mouthfeel (28, 29). Tribology captures the physical basis of mouthfeel consisting of processes such as viscosity, saliva interactions, adsorption, surface properties, and wear. It serves as an important tool to assess the *in vitro* oral breakdown trajectory of foods and beverages. Complexity of taste perception and contributors to palatability/taste cover a wide spectrum ranging from factors directly related to the drug product to extrinsic factors such as cultural background and dietary preferences. While taste panels can address certain sensory aspects, routine testing of formulations in taste panels, particularly in special populations such as pediatrics and geriatrics will be difficult to conduct. An electronic tongue (e-tongue) was first developed in late 1980s/early 1990s to support formulation development/improvement (30). Typical areas of use for the e-tongue are: taste masking and formulation development, comparative studies evaluating predictive ability, and bitterness assessment and attenuation. In addition, the e-tongue is used for characterizing taste masking attributes of solid oral dosage forms (e.g., taste masking as a function of time) and as a tool to determine the duration of formulation taste masking (31). The E-tongue's application in the food and pharmaceutical industries is continuing to grow as evident by the increase in interest and publications over time despite challenges (e.g., sensor response, reference standards, differences in the volume of liquid for electronic tongue/taste sensor vs. mouth, etc.).

Several key messages and recommendations were discussed at the session. With respect to discussions on science and methods for assessing mouthfeel (e.g., texture, tribology) and palatability (e.g., taste masking, e-tongue), information obtained with *in vitro* methods is most valuable in early formulation development (i.e., screening). Further, no single method can replace *in vivo* assessments. While all methods are complementary, methods/tools bring most value when they are used correctly and users manage expectations. There are opportunities for trans-disciplinary learning for formulation development that can be harnessed with continued dialogue with other industries (e.g., food, consumer, human and animal healthcare), academia, and regulatory agencies. There is a need for more venues for open discussion and sharing of knowledge and experiences. There is also a need for continued research and collaboration on how to further apply *in vitro* methods for understanding and improving mouthfeel and taste.

Content Uniformity

Uniformity of dosage units (UDU) can be demonstrated by content uniformity (CU) or weight variation based on drug loading in the products. Proper methods to ensure CU are of particular interest for products with low drug loading and/or narrow therapeutic indices. The draft "Guidance for Industry - Powder Blends and Finished Dosage Units – Stratified In-process Dosage Unit Sampling and Assessment" was withdrawn in 2013 because it no longer reflects the FDA's current thinking. The United States Pharmacopoeia (USP) <905> Uniformity of Dosage Units only provides limited assurance of the tested batch due to the lack of a statistical sampling plan. Therefore, there is an urgent need for alternatives to the existing CU methodology and stratified sampling.

The industry wants flexible sample size and acceptance criteria, especially considering the increased adoption of process analytical technology (PAT) and continuous manufacturing. The zero tolerance criteria prescribed by USP <905> is unproductive. USP recognizes these needs and challenges, and is actively exploring how to consider manufacturing data that indicates high

probability of final product compliance. For instance, USP expert panels and committees were formed to discuss real time release testing and large “N” sampling.

In the meantime, ISPE has proposed a framework following the guideline prescribed by ASTM E2709/E2810. Such a framework offers: (i) increased confidence that future samples drawn from the batch will comply with USP <905> and (ii) linkage of blend and content uniformity covering all three phases of the manufacturing process (i.e., process design, process qualification, and continued process verification). In addition, research has shown the significant advantage of using PAT to ensure and enhance blend and content uniformity. PAT tools can not only provide in-depth product and process understanding, but also facilitate appropriate sampling and enhance statistical confidence. Regarding statistical considerations for sampling and defining acceptance criteria, different sampling strategies are available (e.g., simple random sampling, stratified sampling, systematic sampling). It is important to note that random sampling may not be able to provide the estimation of between/within location variability. Distribution of the data needs to be determined because it will dictate the data analysis method. The acceptance criterion should be clinically relevant; it needs to fit the required product quality level. For instance, the acceptance criterion for a low drug loading and high potency product may be different from that of a high drug load product. It is important to discuss content uniformity acceptance criteria and sampling plans with regulatory authorities early on. Once deemed acceptable, such acceptance criteria and sampling plans may be updated or revised throughout the lifecycle of the product when more advanced manufacturing and process controls are adopted.

Science of Tech Transfer/Scale-Up

Moving from lab and pilot scale development work to commercial manufacturing scale can proceed on schedule and within budget or it can turn into an expensive set-back. Unexpected costs, delayed launch, lost revenue, and drug shortage may occur if process control and product quality problems arise. However, the likelihood of successful scale up and tech transfer to the commercial plant can be greatly increased by employing a multidisciplinary approach focused on

fundamental pharmaceutical science, engineering expertise, innovative materials science methodology, and advanced computer-based predictive tools.

At the conference, case studies demonstrated effective use of mechanical and predictive modeling and simulations in areas such as powder and particle behavior, as well as unit operations such as fluid bed granulation, bi-layer tablet compression, and pan coating. Models and simulations in support of root cause analysis during the product lifecycle and risk mitigation strategies were also presented.

Full scale Design of Experiments (DOEs) to achieve mechanistic product and process understanding can be expensive and impractical when numerous variables are present. Scale up and scale down rules, as well as identification of scale-independent parameters, are useful. Additionally, the application of mathematical modeling, simulation, and advanced analytics can provide insight into behaviors of materials and structures that enable cost effective design and optimization of manufacturing processes. Instead of large scale DOE runs involving more than ten operating parameters for example, commercial runs can validate model predictions. Thus, scale up risk is mitigated.

Cost savings are realized as less material is used in the modeling experiments and commercial plant time is reduced while commercial process parameters are predicted. However, effective use of modeling and simulation requires skilled staff. The pharmaceutical industry could recruit from other sectors that routinely use these techniques to bring in the essential skill sets. From a regulatory perspective these techniques are highly encouraged. The use of predictive models and simulation are acceptable approaches to product and process development, as well as in manufacturing to support real time release testing (RTRT) and innovative technologies like continuous manufacturing.

By providing sufficient information and data in support of the scaled up process, regulatory review is more efficient and IR cycles are minimized. Sponsors should consult regulatory guidance

about the type and extent of model information to include in regulatory submissions. An example of such information is in the FDA-EMA QbD material (32). Standardization of models is not common in the pharmaceutical industry, but sharing models and developing model standards could aid industry development work and facilitate regulator review of submission. Greater adoption of multidisciplinary approaches using predictive modeling and simulation in research and development will improve scientific product and process understanding. Ultimately this will lead to cost-effective, successful tech transfer and scale-up, and increased confidence in the manufacturing system overall.

Manufacturing and Quality Assurance

How to Prevent, Detect, and Respond to Data Integrity Events

Data integrity is the degree to which a collection of data is complete, consistent, and accurate. Data integrity provides the foundation of pharmaceutical quality. Without reliable data, the 21st Century vision that manufacturers produce high quality drugs without extensive regulatory oversight cannot be realized. Breaches of data integrity erode confidence of regulators and the public. Two main areas of concern regarding data integrity are: (i) supplying data to a health authority as a result of an inspection and (ii) providing data as part of a regulatory submission. Data integrity issues can occur at any time and in any place to any company. Data may be unreliable due to sloppiness and inadvertent errors. A pattern of errors can raise questions about the overall reliability of the data. Common causes of data integrity problems include:

- Quality system does not have adequate controls and oversight of manufacturing operations and processes;
- Business and performance pressure such as time pressure, inventory demands, desire to meet metrics/goals;
- Cultural pressure such as deliberated attempt to hide errors and desire to deflect accountability;
- Inadequate processes and technology such as insecure computer systems and lack of

training.

In responding to the data integrity problems, the firm needs to conduct comprehensive investigations to uncover root causes, determine the effect of deficient documentation practices on the quality of the drug product released for distribution, and develop a management strategy to detail the firm's global corrective action and preventative action plan. At the end, the FDA may re-inspect the firm to prevent the reoccurrence of data integrity problems.

In summary, the firm should maintain accuracy, reliable design, consistent intended performance of record systems, and both paper document systems and computerized systems. Both paper and electronic data should be controlled to ensure authenticity, integrity, confidentiality, retrievability, accuracy, consistency, and completeness throughout the data lifecycle. Hand-written and electronic signature controls should be in place to ensure legal binding. Ultimately, effective quality systems and management governance assure data integrity.

Continuous Manufacturing

Continuous manufacturing is an emerging technology that offers opportunities for all stakeholders: patients, regulators, and industry. Potential benefits include: (i) reduced variability and increased reliability through the adoption of precise control; (ii) reduced costs due to the reduction in equipment footprints and increased process efficiency; (iii) reduced processing time per unit dose (minutes vs. days); (iv) elimination of scale-up bottlenecks leading to more agile and responsive supply chains; and (v) increased capability to rapidly respond to drug shortages, emergencies, and patient demand to ensure a consistent supply of high quality medicines. The implementation of continuous manufacturing does present challenges to both industry and regulatory bodies, but quality risk management provides a framework for identifying and communicating approaches for addressing these challenges.

Deep process understanding provides a basis for identifying and evaluating hazards and failure modes and the scientific foundation for designing controls to mitigate these risks. One of the key areas of understanding in process design and control strategy development is the understanding of material flow. Knowledge of system dynamics can be used to predict how disturbances propagate through the process. In this way knowledge of system dynamics can be used to track and separate conforming and non-conforming product. Capturing the understanding of system dynamics may include the development of process models.

The control strategy for a continuous process should be designed to mitigate product quality risks in response to potential variations over time. Criteria for establishing a state of control will depend on the control strategy implementation options (Fig. 6). For continuous manufacturing, the control strategy may need to integrate more advanced approaches to mitigate the identified risks such as: (i) the establishing criteria for state of control (e.g., start up and shutdown); (ii) in-process monitoring (including PAT); (iii) process controls (including model-based controls); (iv) material tracking and diversion schemes for non-conforming product, (v) analysis of large data sets for trending and continuous improvement, and (vi) real-time release testing. The design of the control strategy should ensure uniform character and quality within specified limits over a range of production time periods, amount of material processed, or production variation (e.g., different lots of feedstock). Thus, the control strategy provides flexibility for the proposed batch definition. Manufacturers have been able to apply a variety of batch definitions based on specific processes and drivers and are still able to comply with the applicable regulations.

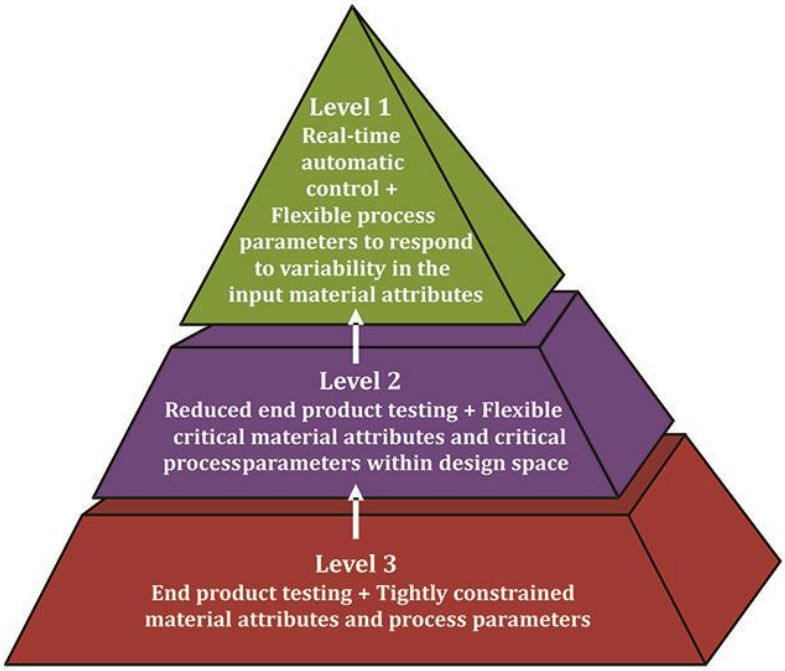

Figure 6. Control strategy implementation options (33). There are three levels of control strategy implementation: Level 1 - active control system with real time monitoring of process variables and quality attributes (reliant on active process controls system); Level 2 - operation within established ranges (multivariate) and confirmed with final testing or surrogate models (reliant on process monitoring and diversion of nonconforming material); and Level 3 - unlikely to be operationally feasible for addressing natural variance in continuous manufacturing without significant end product testing.

It was noted though that regulatory expectations are the same for continuous manufacturing as for traditional batch manufacturing regarding the science and risk-based approaches and control of processes. Dialogue and alignment between industry and regulators is important for successful implementation, and there are multiple opportunities for early engagement with the FDA. While significant progress has been made, some regulatory and quality aspects are still developing so there is still work to be done, such as:

- Application of continuous process verification versus validation campaigns;
- Integrated product specifications and dossier content for integrated end-to-end processes (i.e., raw materials to drug product);

- Application of existing specific guidance needs to be evaluated (e.g., SUPAC guidance);
- Determination of the start of shelf life.

How to Monitor, Control, and Improve Product Quality using Process Capability

A high quality drug product has been defined as a product free of contamination and reproducibly delivering the therapeutic benefit promised in the label. Free of contamination is largely a CGMP focus while reproducibly delivering the therapeutic benefit promised in the label is essentially the QbD focus. Therefore, the pharmaceutical quality could be considered as a function of QbD (science) and CGMP. The objectives of QbD include: (i) achieving meaningful product quality specifications based on assurance of clinical performance and increased process capability and (ii) reducing product variability and defects by enhancing product and process design, understanding, and control (33).

Process capability is defined as the natural or undisturbed performance after extraneous influences are eliminated. A state of statistical control (i.e., stable state) means that the process exhibits no detectable patterns or trends and hence the variation seen in the data is due to random causes and is inherent to the process. Process capability is a leading, useful indicator of product quality. It represents how well a given process could perform when all special causes have been eliminated. Process capability also bears a relationship to supply chain management. It can be used as an indicator for supply chain dependability and to inform inventory management.

Measuring and achieving robust process capability requires systematic approaches. As articulated in ICH Q10, the quality system supports the objectives to achieve product realization, establishes and maintains a state of control, and facilitates continual improvement (34). A philosophy of continuous improvement has been described as operational excellence. The foundation of achieving operational excellence is a focus on quality, which subsequently delivers benefits in dependability, speed, and ultimately cost.

Firms recognize the benefits of understanding and controlling variability in processes and product. Manufacturing in many different industries can be analyzed using the number of standard deviations between the process mean and the nearest specification limit. This measure of process capability is often given the value of sigma. The pharmaceutical industry historically manufactured at one to two sigma, with a significant focus on compliance and meeting specifications. However, spurned by recent quality initiatives, six sigma is now possible in the pharmaceutical industry. Indeed some companies, such as Lilly and Amgen, are either achieving or working toward six sigma. Firms are realizing benefits in fewer errors, faster cycle times/more productivity, and less waste/loss (as shown in Fig. 7). Achieving high sigma performance takes time and requires persistent support from leadership on improving poor performing products and processes. Developing deep technical understanding and control, and working on flawless execution and human error prevention are key contributors to success. There are challenges in achieving high sigma including regulatory specification limits that were often set based on limited process capability data, the small number of lots that allow the determination of steady state, and investments and regulatory changes to manufacturing processes and analytical methods. Strong partnerships between industry and regulatory agencies to remove barriers are an important part of achieving the vision of maximally efficient pharmaceutical manufacturing.

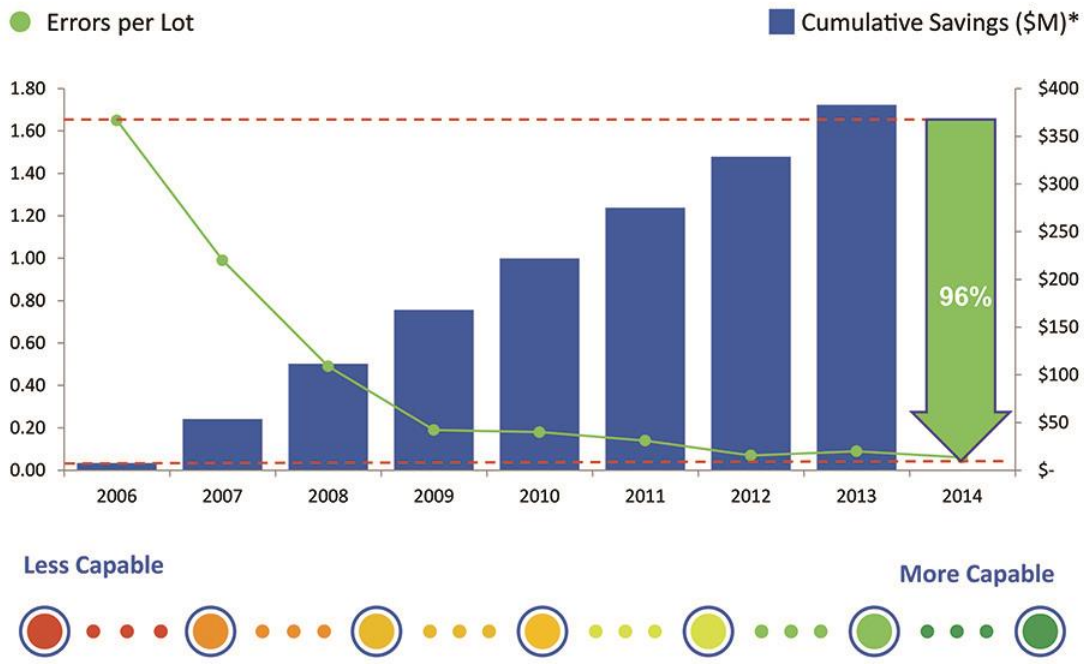

Figure 7. The benefits of six sigma performance. By driving six sigma performance, Amgen reduced error rate by 96% and realized $400M cumulative saving.

How to Identify Critical Quality Attributes and Critical Process Parameters

In the determination of what is really critical in a process, one has to "begin with the end in mind" starting with the Quality Target Product Profile (QTPP). The QTPP prospectively summarizes elements of drug quality, safety, and efficacy, and thus forms the basis for development of the Critical Quality Attributes (CQAs). CQAs are then used to make design and optimization decisions and to identify critical material attributes (CMAs), critical process parameters (CPPs), and refinement of the control strategy through a continuum of risk assessment and structured experimentation.

Recent case studies by industry have focused on identification of CPPs based on CQAs and mechanistic process and product understanding. Those studies have shown that focusing on

one product and process unit operation to assess control space can be misleading, and best results have been achieved in striving for deeper mechanistic understanding of the product and process. Other industry efforts have focused on development of approaches utilizing statistical tools for consistency, while still incorporating scientific judgment and a holistic view of the control strategy. In utilizing such statistical approaches, it is important to determine that the CPP-CQA relationship is not only statistically significant, but also practically significant. Generic drug sponsors are usually faced with completely different timelines and drivers as compared to NDA product development. In the generic industry, where leveraging documented prior knowledge is advantageous, QbD implementation has been shown to be both scientific and strategic, and should be fully integrated in product development.

Drug sponsors who claim that “none of the drug quality attributes are critical because of fixed material attributes and process parameters for all key processing steps” will often hear the FDA respond that “all material attributes and process parameters are potentially critical as a result of limited characterization of the sources of variability and inadequate understanding of the impact of CMAs and CPPs on the drug product CQAs.” By contrast, sponsors that have implemented significant control of the CQAs with in-process or at-line measurements (e.g., via NIR spectroscopy) will find that the FDA will focus the review on the control of critical steps and intermediates (e.g., using the NIR test method).

Summary

The October 2015 FDA/PQRI Conference on Advancing Product Quality provided a forum for the exchange of ideas focused on drug product quality between regulatory agencies, the pharmaceutical industry, and academia. Key topics of the 2015 conference were: (i) emerging regulatory initiatives; (ii) regulatory submission, assessment, and inspection; (iii) product and process development; and (iv) manufacturing, risk management, and quality assurance. Key discussion points and recommendations for each track and session have been captured. With powerful advancements in product quality encompassing regulatory, industrial, and

technological elements, an era of rapidly improving pharmaceutical quality is underway. At the conference one theme prevailed through all sessions: regulators, industry, and academia are aligned in their desire for drug product quality on behalf of the ultimate stakeholder – the patient.

Acronyms and Abbreviations

3D	**Three Dimensional**
ANDA	**Abbreviated New Drug Application**
API	**Active Pharmaceutical Ingredient**
ASTM	**American Society for Testing and Materials**
BCS	**Biopharmaceutics Classification System**
BLA	**Biological License Application**
CGMP	**Current Good Manufacturing Practice**
CMA	**Critical Material Attribute**
CMC	**Chemistry Manufacturing and Controls**
CPP	**Critical Process Parameters**
CQA	**Critical Quality Attribute**
CU	**Content Uniformity**
DLS	**Dynamic Light Scattering**
DOE	**Design of Experiment**
EMA	**European Medicines Agency**
EWG	**Expert Working Group**
FDA	**Food and Drug Administration**
GDUFA	**Generic Drug User Fee Amendments**
HCl	**Hydrogen Chloride**
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	
IND	**Investigational New Drug**
IQA	**Integrated Quality Assessment**
IR	**Immediate Release**
IR	**Information Request**
ISPE	**International Society for Pharmaceutical Engineering**
MIT	**Massachusetts Institute of Technology**
NDA	**New Drug Application**
NIPP	**New Inspection Protocols Project**
NIR	**Near-Infrared Spectroscopy**
OPQ	**Office of Pharmaceutical Quality**
PAI	**Pre-Approval Inspection**
PAT	**Process Analytical Technology**
PDUFA	**Prescription Drug User Fee Act**
PHS	**Public Health Service**
PQRI	**Product Quality Research Institute**

PQS	**Pharmaceutical Quality System**
QbD	**Quality by Design**
QMS	**Quality Management System**
QRM	**Quality Risk Management**
QTPP	**Quality Target Product Profile**
RPM	**Revolutions per Minute**
RTRT	**Real Time Release Testing**
SUPAC	**Scale-Up and Post-Approval Changes**
UDU	**Uniformity of Dosage Units**
USP	**U.S. Pharmacopeial Convention**

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