Life & Health

Pharmaceutical Communiqué

Q4 2013

WHERE IS CDER GOING IN THE NEXT 5 YEARS?

There's value in knowing how the Center for Drug Evaluation and Research (CDER) plans to meet its mission over the next five years and the Center's newly released Strategic Plan 2013-2017 provides some help in that area. CDER sets the foundation for the strategic plan early in the report, explaining that its mission can "be expressed in terms of three long-term objectives for human drugs ...." Those three objectives:

- Promoting public health by helping to ensure the availability of safe and effective drugs;
- Protecting public health by promoting the safe use of marketed drugs;
- Protecting public health by helping to ensure the quality and integrity of marketed drug products.

CDER identifies three strategies to achieve the third objective, which deals specifically with drug quality. First, secure the global supply chain to help ensure that drug integrity is maintained and that drugs are being manufactured and

WHERE IS CDER GOING IN THE NEXT 5 YEARS? *(Continued)*

distributed to conform to established quality standards. Second, improve drug quality oversight capacity through expanded use of risk-based methods. Third, promote public and stakeholder awareness of drug quality and integrity issues through effective consumer communications.

The Center's oversight of drug manufacturing and quality has multiple components. Among them: conduct of pre-approval manufacturing facility inspections; facility inspections for compliance with current Good Manufacturing Practices (cGMPs); surveillance to detect health fraud or other product issues; and monitoring and enforcement to help ensure the authenticity and integrity of drug products, the availability of drugs of acceptable quality, and the safety of the global drug supply chain.

The strategic plan goes on to identify the four strategies CDER has identified for accomplishing its goals over the next five years. The strategies are not new but they do reinforce concepts that have been reinforced in speeches by senior FDA officials for the past several years:

- Smarter regulation, which CDER expects to result in regulatory decision processes that "... feature enhanced predictability, transparency and efficiency."
- Scientific innovation focuses on addressing scientific uncertainties that contribute to failures of drugs in development, poor predictability in individual patient response, unexpected safety problems and variability in drug quality.
- Lean management. CDER identifies several anticipated project areas for cross-cutting processes for streamlining and adding value. At the end of FY 2013, anticipated project areas include cross-cutting processes to ensure drug quality, relate to regulatory compliance and enforcement, and address drug safety issues. These initiatives are slated to continue through FY 2015
- Business modernization initiatives include the digitization of CDER data including regulatory submissions, regulatory review work and work products, and drug regulatory work process tracking. Major projects under the category of drug quality and compliance were launched in FY 2013 and scheduled to continue through FY 2015. They include integrated master data management, risk-based inspection management, pharmaceutical quality surveillance and Orange Book modernization.

CDER emphasizes its commitment to engage stakeholders, including the Pharmaceutical industry, in meeting its target goals. The report states, "The four major strategies we plan to pursue – smarter regulation, scientific innovation, lean management and business modernization – will increase our Center's efficiency and effectiveness, and acknowledge the importance of engaging stakeholders to meet our mission challenges."

LESSONS LEARNED ABOUT QUALITY-BY-DESIGN

Both FDA and the European Medicines Agency (EMA) have expressed support for Quality-by-Design (QbD) as a means of ensuring consistency of US and EU implementation of ICH guidelines including Q8, Q9, Q10 and Q11. In 2011, the two agencies launched a pilot program for parallel assessment of QbD applications. Recently, FDA and EMA released a review of lessons learned from the first parallel assessment. The Q/A section of the document highlights the agencies' expectations in regulatory submissions for Quality Target Product Profiles (QTPP). Equally important, however, the Q/As provide some insight into the agencies' perspective toward quality regulations and compliance.

Takeaways about the expectations of FDA and EMA:

1. The QTPP submitted by the applicant describes prospectively the quality characteristics of a drug product that should be achieved to ensure the desired quality of a finished product.
2. Applicants are expected to provide a list of Critical Quality Attributes (CQAs) for drug substances, finished products and excipients when relevant and additional data about how the drug substance and excipient CQAs relate to the finished product CQAs.
3. The description of all parameters that have an impact on a CQA should be classified as critical. A critical factor is defined as a factor that led to failure during experimentation.
4. The agencies expect process descriptions to be comprehensive and describe process steps in a sequential manner including batch size and equipment type. Process parameters included in the manufacturing process description should not be restricted to critical ones; all parameters that have been demonstrated during development as needed to be controlled or monitored during the process to ensure that the product is of the intended quality need to be described.

FDA and EMA considered the pilot program to be useful in sharing knowledge, facilitating a consistent implementation of the ICH guidelines and harmonizing regulatory decisions. Pharmaceutical companies should expect to see the results of the assessment process reflected in new regulatory concepts moving forward.

FIGHTING THE EFFECTS OF BUSINESS DECISIONS ON QUALITY

Quality departments in Pharmaceutical companies carry the responsibility for product quality and compliance. Unfortunately, they often lack the resources, authority and input needed to avoid problems that can be caused by business decisions or operations outside the quality "silo." Too often, that situation changes only when a quality problem emerges and corporate attention snaps to the quality department.

A number of situations can be seen as "red flags" of possible risks, either short-term or over the long term. Quality professionals who recognize these signs can anticipate the potential consequences and respond proactively. Here are some signals that might indicate risks to product quality:

- **Facility maintenance budgets are cut or are at unrealistic, low levels**. Several recent FDA inspections have cited violations that could indicate inadequate training or performance of personnel responsible for essential maintenance functions including those related to environmental controls. A review of FDA Warning Letters illustrates contamination issues including insect parts and metal shavings in finished Pharmaceutical products. Not all contamination issues reach that point before being identified. Following one inspection, FDA noted that numerous HEPA filters, supporting grid work, screens and screen tracks contained varying amounts of discolored areas, chipping paint and dark material later revealed to be mold. Possible causes include a drop in the maintenance budget, staff reductions in the maintenance department or aging facilities that would reasonably require regular updating and repair.
- **The corporate "quality message" does not match the company's internal practices**. Some of the most serious quality violations have occurred because the corporate messaging to external stakeholders – including transparency – is not carried through in internal operations. Recently, a company recognized for its expressed commitment to quality and compliance was cited for multiple violations under the general category of "... delayed, denied, limited an inspection or refused to permit the FDA inspection." The FDA investigator noted specific actions by the company's QA Officer, QC Analyst, Production Head and Vice President of Manufacturing. Actions during the inspection included hiding records, dumping contents from vials in the washing area, providing inaccurate information and impeding the investigator in inspecting production sites the investigator asked to see.

FIGHTING THE EFFECTS OF BUSINESS DECISIONS ON QUALITY *(Continued)*

- **Business functions that are organized in separate silos inhibit communication, collaboration and consistent application of policies that can affect quality**. One of the most frequently cited observations of FDA investigators is the company's failure to ensure that employees have the appropriate training, education and experience to perform their job functions. Ensuring employee qualifications involves hiring, identification of knowledge gaps, training and testing, yet these functions may be under the jurisdiction of departments including human resources, compliance and quality. Well-established communication and coordination among those departments is particularly important during events such as corporate downsizing, staff increases, rapid expansion of production sites, acquisition of new facilities and changes in processes.
- **Inadequate communication and collaboration with other corporate facilities**. Companies that lack an established mechanism for sharing information about production issues, observations by regulatory agencies, quality problems or poor testing results following training are at risk of receiving a letter from FDA with the warning that violations uncovered at one facility are identical to those found at another facility owned by the company. FDA has become increasingly impatient with such violations, issuing some version of the following, which was recently issued to a multi-site Pharmaceutical company, "These identical cGMP violations demonstrated a lack of adequate process controls and raised serious questions regarding your corporation's quality and production systems." The result of those repeat violations was an import alert and product detention for two facilities producing products for the US market.
- **An "add-on" or "across-the-board" approach to training can create training overload, leading employees to focus only on passing the test without applying the new information**. A worker in today's sophisticated manufacturing plants may be responsible for understanding and applying hundreds of Standard Operating Procedures that are revised several times a year. When training elements are developed and conducted independently, rather than in a need-specific approach that targets the knowledge needs of individual job functions or employees, companies can waste scarce corporate resources, employees' time on the job, and employee receptivity to new information. Effective training requires a cohesive program that includes testing of employees to identify understanding, the provision of remedial training for employees who fail to demonstrate competency and oversight to quickly identify those employees, departments or training elements that fail to deliver the required results.

Quality Directors are frequently excluded from corporate planning and decision-making that will affect the quality function. While they may not be able to change that, they may be able to anticipate many of the quality impacts of corporate decisions, policies and programs, and initiate actions that could mitigate the effect of such actions on product quality and compliance.

About UL EduNeering

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UL EduNeering develops technology-driven solutions to help organizations mitigate risks, improve business performance and establish qualification and training programs through a proprietary, cloud-based platform, ComplianceWire®.

For more than 30 years, UL has served corporate and government customers in the Life Science, Health Care, Energy and Industrial sectors. Our global quality and compliance management approach integrates ComplianceWire, training content and advisory services, enabling clients to align learning strategies with their quality and compliance objectives.

Since 1999, under a unique partnership with the FDA's Office of Regulatory Affairs (ORA), UL has provided the online training, documentation tracking and 21 CFR Part 11-validated platform for ORA-U, the FDA's virtual university. Additionally, UL maintains exclusive partnerships with leading regulatory and industry trade organizations, including AdvaMed, the Drug Information Association, the Personal Care Products Council and the Duke Clinical Research Institute.