Life & Health

Pharmaceutical Communiqué

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UNDERSTANDING THE EU GMP INSPECTION

Note: The following excerpt is part of a new course entitled "EU Directives and Inspection Readiness" from UL EduNeering, scheduled to be released in December 2014. Authored by the experts at consulting firm EduQuest, this course will be available to all subscribers of the GMP Libraries.

All pharmaceutical products – APIs and finished medicines – manufactured or supplied to 28 member countries of the EU must be produced according to Good Manufacturing Practices (GMPs) established in EU Directives and Guidelines. Regular regulatory inspections are conducted on these facilities to ensure that they comply with GMP requirements. Serious GMP deficiencies may result in closed facilities, banned products and drug shortages that can affect millions of patients.

(continued...)

UNDERSTANDING THE EU GMP INSPECTION *(Continued)*

EU Regulatory Framework

The EU has several Directives that collectively regulate the development, market authorization, manufacture and distribution of medicines for human use. GMP regulations are contained in EudraLex Volume 4:

- **Part 1 contains nine chapters that address different aspects of GMPs for medicinal products.** Those chapters address pharmaceutical quality systems, personnel, premises and equipment, documentation, production, quality control, outsourced activities, complaints and product recalls and self-inspection.
- **Part 2 includes the basic requirements for active substances** that are used as starting materials in the production of finished medicines.
- **Part 3 includes GMP-related documents** such as ICH guides on quality risk management and Pharmaceutical quality systems.
- **19 individual annexes provide details on specialized areas of activity**, including the manufacture of sterile products, the use of computerized systems and sampling of starting and packaging materials.

Each of the 28 member states of the EU is required to identify a Competent Authority, which is the body that holds responsibility for ensuring compliance with the EU's requirements and standards for medicinal products. Before a medicinal product can be supplied to member states, the supplier must receive a marketing authorization that is granted after the member state's Competent Authority or the European Medicines Agency (EMA) completes a detailed evaluation of all scientific data on the safety and efficacy of the product.

To be sold in the EU, both the product and the location at which it has been manufactured must have earned a manufacturing authorization. In order to receive marketing authorization, the location where the product is manufactured must be regularly inspected by the Competent Authority in the relevant member state.

GMP Inspection Triggers

There are several triggers for a GMP inspection:

First, a company that submits an application to market a medicinal product in a member state or number of states will normally be subject to an inspection of the manufacturing activities detailed in its marketing application. These inspections are very serious: If the visiting inspector is not satisfied, the application will not be approved and may extend to other companies identified in the application, including contract manufacturers, active ingredient suppliers or laboratories.

Routine inspections of companies with manufacturing authorizations can also be expected, typically every two to three years. These inspections are undertaken to confirm compliance with GMPs and other requirements, such as marketing authorization provisions. Although these inspections are usually scheduled by inspectors to ensure that key staff is present, they may be unannounced.

Additional inspections may occur if the Competent Authority or EMA has reason to question a product's safety, efficacy or GMP compliance. Questions can arise because of reports of defective products, a large number of market complaints or product recalls. In these cases, the inspector will require confirmation that effective corrective and preventive actions have been taken. In some cases, additional inspections will be required when GMP deficiencies are identified during routine inspections. The follow-up inspector will require confirmation that any deficiencies noted in the original inspection have been resolved. Finally, a request by the company to change a marketing application – a proposal to revise a manufacturing process, for example – will typically trigger an inspection. The company can expect a denial to its request unless the inspection is satisfactory.

UNDERSTANDING THE EU GMP INSPECTION *(Continued)*

Understanding the Inspection Process

Most inspections consist of four phases:

- **The Introductory Meeting:** The inspector will confirm the purpose and scope of the inspection and should indicate what they want to see and what type of documentation they require. This phase of the inspection gives the inspector the opportunity to meet with senior company personnel who can provide details of the site and its operations. The meeting can also provide company personnel with insight into the inspector's approach and potential concerns.
- **Inspection:** Inspectors can request to see the actual manufacturing activities, review related documentation and interview managers and staff related to the activities. Inspectors can also ask for information that is not held on the site they are visiting (for example, information held by a supplier). It is important to recognize that inspectors are highly trained and knowledgeable about the law and the pharmaceutical production process. All personnel likely to be questioned by an inspector should have the necessary experience and training so they can respond clearly, concisely and accurately. If an individual cannot answer a question asked by the inspector, he or she should refer the inspector to the appropriate person. Nobody should attempt to answer a question "on the fly."
- **Close-Out Meeting:** Inspections routinely end with reviews of the inspector's findings and discussion about what will be examined the following day. The final meeting at the end of the inspection provides an opportunity for the company to correct any mistakes or misconceptions the inspector may have.
- **Post-Inspection Report:** A written confirmation of the identified deficiencies will be sent to the company. Depending on the severity of the deficiencies and the company's response to them, a GMP certificate confirming compliance with GMP will be issued – or action may be taken against the company, including suspension or limits on the manufacturing authorization.

Inspections and Compliance

A regulatory inspection will confirm – or disprove – compliance with GMPs and other legal requirements. Successful inspections don't "just happen." They are the result of careful planning and implementation. Particularly important are the following activities:

- Ensuring that all documentation relating to quality systems is up-to-date, accurate and easily accessible for review;
- Training and documentation of all training activities required for GMP compliance;
- Training of all personnel in the inspection process, including what types of information are likely to be asked, how to respond to an inspector's request and potential risk areas;
- Maintenance of documentation related to suppliers and contractors, including audits and technical agreements;
- Sampling procedures and facilities;
- Maintenance of premises and equipment, including routine housekeeping.

The EU, like the US, Australia and dozens of other countries around the globe, is increasing its scrutiny of medical products manufactured, distributed and prescribed in its member states. Companies that manufacture or sell medicines in the EU should pay careful attention to the requirements and procedures involved in GMP inspections. Doing so can be the difference between participating in the EU market and being shoved to the sidelines.

QUALITY CONTROL AND THE FALSIFIED MEDICINES DIRECTIVE

UL EduNeering has been tracking the 2011 Falsified Medicines Directive, published by the European Parliament and the Council of the European Union. We are evaluating this topic as a potential course for the future.

The 2011 Falsified Medicines Directive was designed to prevent the flow of fake medicines into Europe's legitimate supply chain. Under the Directive, the European Commission (EC) was charged with developing the technical details for member states to implement the Directive. The deadline for the EC was 2014 with a mandate that member states execute the Directive three years later.

This directive will affect all manufacturers, distributors and wholesalers of pharmaceutical products in the EU. Both finished drugs and APIs are included under the Directive, regardless of where they have been produced. While the Directive is most often associated with the tracking systems that include bar codes and tamperproof packaging, it is worth reviewing some of the important quality-related provisions contained in the Directive before its 2017 implementation deadline.

Falsified or Counterfeit

Both falsified and counterfeit medicines are safety issues for patients – but they are not synonymous. Falsified medicines are, quite simply, fake medicines. Here's what the European Commission says about falsified medicines: "Falsified medicines are fake medicines that pass themselves off as real, authorized medicines. Falsified medicines might contain ingredients, including active ingredients, which are of bad quality or in the wrong dose – ether too high or too low. As they have not been properly evaluated to check their quality, safety and efficacy – as required by strict EU authorization procedures – this could be detrimental to your health." Tragically, falsified medicines have been and continue to be responsible for many deaths, particularly when they are used to treat life-threatening conditions such as malaria, HIV/AIDS and cancer. Conversely, counterfeit medicines are those that do not comply, according to the EMA, "... with intellectual-property rights or that infringe trademark law."

Definitions under the Directive are important. An active substance is any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product. An excipient is any constituent of a medicinal product other than the active substance and packaging material. Specifically, a falsified medicinal product is one with a false representation of:

- Its identity, including its packaging and labeling, its name or its composition in regard to any of its ingredients including excipients and the strength of those ingredients;
- Its source, including its manufacture, its country of manufacturing, its country of origin or its marketing authorization holder; or
- Its history, including the records and documents relating to the distribution channels used.

QUALITY CONTROL AND THE FALSIFIED MEDICINES DIRECTIVE *(Continued)*

Finished Drugs and Active Substances

The short-hand version of the Directive's quality requirements is this: Products – whether finished medicines or active substances – must be manufactured under GMP conditions and distributed under GDP standards. It is these two requirements that most directly affect the quality departments of finished medicines, APIs and excipients.

While the Chief Compliance Officer will typically be responsible for assuring compliance with the extensive authorization, certification, tracking and documentation requirements of the Directive, quality directors are required to implement policies and procedures to ensure that APIs, excipients and finished products comply with GMP requirements. Meeting these quality requirements will, in turn, depend on training to continually increase employee knowledge. This will include regularly updated, delivered and tested SOPs and other compliance materials; effective controls for compliance procurement, acceptance and use of APIs and excipients; due diligence of suppliers, wholesalers, distributors and other relevant third parties; and procedures to quickly and accurately identify quality inadequacies.

If the requirements under the Directive were not complex enough, an added challenge is thrown into the mix as member states work to transpose the Directive into their own national laws and regulations. The deadline set under the Directive for member states to incorporate the Directive into their own laws was 2013; several member states have still not met that deadline. Even without the "missed deadlines," companies may face added issues because members states may interpret the Directive differently – and their requirements may differ somewhat.

The Falsified Medicines Directive is a significant step forward in being able to track the manufacture of substances and finished drugs. It is also an added challenge for the quality departments of Pharmaceutical companies not only to ensure the quality of their own products but to heighten their attention to the quality of active substances and excipients used in their products. Meeting that added challenge will require a vigorous focus on training that includes the specific requirements of the Directive but places equal weight on a continually reinforced emphasis on SOPs and GMP compliance.

If you have interest in a standard course covering this EU Directive, please contact us at EduNeeringInquiry@UL.com.

ICH Q11: EXTENDING QUALITY STANDARDS WORLDWIDE

UL EduNeering currently offers several courses to help learners understand International Conference on Harmonization (ICH) Guidance, specifically Q7 through Q10. We are now evaluating the development of a new course on ICH Q11, which is entitled, "Development and Manufacture of Drug Substances."

This guidance builds on concepts described in earlier ICH guidances including Q8 (Pharmaceutical Development), Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System). With Q11, ICH defines approaches to the development of the manufacturing process for drug substances.

In November 2012, the US Food and Drug Administration (FDA) accepted the ICH Q11 guidance and released its own Guidance for Industry: Q11 Development and Manufacture of Drug Substances.

According to FDA's guidance, "A company can choose to follow different approaches in developing a drug substance. For the purpose of this guidance, the terms *traditional* and *enhanced* are used to differentiate two possible approaches. In a traditional approach, set points and operating ranges for process parameters are defined and the drug substance control strategy is typically based on demonstration of process reproducibility and testing to meet established acceptance criteria. In the enhanced approach, risk management and scientific knowledge are used more extensively to identify and understand process parameters and unit operations that have an impact on critical quality attributes (CQAs) and develop appropriate control strategies applicable over the lifecycle of the drug substance, which might include the establishment of design spaces. As discussed in ICH Q8 for drug products, a greater understanding of the drug substance and its manufacturing process can create the basis for more flexible regulatory approaches."

ICH Q11: EXTENDING QUALITY STANDARDS WORLDWIDE *(Continued)*

Not surprisingly, there are multiple provisions contained in the Guidance. Particularly important to quality personnel are the approaches to development. Either the traditional approach or an enhanced approach – or a combination of both – to drug substance development can be chosen but manufacturing process development should include at a minimum:

- Identifying potential CQAs associated with the drug substance so that those characteristics having an impact on drug product quality can be studied and controlled;
- Defining an appropriate manufacturing process;
- Defining a control strategy to ensure process performance and drug substance quality.

An enhanced approach to manufacturing process development would include these additional features:

- Identifying (through, for example, prior knowledge, experimentation and risk assessment) the material attributes (e.g., of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters that can have an effect on drug substance CQAs;
- Determining the functional relationships that link material attributes and process parameters to drug substance CQAs.

Although it is a separate guidance, ICH Q11 follows and adds to earlier quality guidance standards issued by ICH (Q6-Q10). Implementation of the guidelines will require careful consideration of the approach to be taken and how that approach will be implemented throughout the organization. It is worth remembering that the point of Q11 is to control impurities in drug substances and, subsequently, in finished medicines. The process will require corporate resources, significant training and, potentially, a "rethinking" by the quality department of the scope and impact of its responsibilities.

To review our current list of ICH courses, send your request to EduNeeringInquiry@UL.com.

We would also like your thoughts or suggestions for additional course topics related to ICH, WHO or global agencies.

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If you have questions, would like to review our current list of ICH courses, or are interested in developing customized courses for your organization, contact us at EduNeeringInquiry@UL.com.

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