Life & Health

# Pharmaceutical Communiqué

Q2 2015



## ADVANTAGES AND DISADVANTAGES OF SAMPLING METHODS

The Pharmaceutical industry utilizes a variety of sampling methods for cleaning validation. Of these, the FDA has indicated their preference for swab sampling, solvent rinse sampling, rinse solution sampling and in-process monitoring. Advantages range from methods being economical to being easy to use. Disadvantages range from methods being technique-dependent to being invasive.

The advantages and disadvantages are noted on the following page and are also available in our online course, ***Collecting Samples and Establishing Limits for Cleaning Validation*** (PHA54):

- Swab sampling
- Rinse solution sampling
- Solvent sampling
- In-process monitoring

*(continued...)*

## SWAB SAMPLING

| Advantages | Disadvantages |
|---|---|
| 1. Removes non-soluble materials | 1. Is technique-dependent |
| 2. Is adaptable to a wide variety of surfaces | 2. Is not suitable for hard-to-reach locations |
| 3. Is economical | 3. Is an invasive procedure |
| 4. Allows for sampling of controlled areas | 4. May add extra steps |
| 5. Gives data that relates to a specific location | 5. Must determine the percentage of material that is removed from surfaces (recovery) |
| 6. Detects many residues | 6. And the swab material may inhibit recovery |
| 7. And may be performed on equipment that is wet or dry | |

## SOLVENT SAMPLING

| Advantages | Disadvantages |
|---|---|
| 1. Will detect many types of residues | 1. Solvents can be flammable, toxic, or carcinogenic |
| 2. Is not technique-dependent | 2. May require the use of chemical personal protective equipment |
| 3. Allows testing of hard-to-reach areas | 3. There is reduced physical sampling of the surface |
| 4. Allows for sampling of delicate and complex surfaces | 4. Is difficult to specify the actual surface area sample |
| 5. Recovery may not be a significant factor | 5. May require considerable time |
| 6. And may be considered non-invasive | 6. And may be difficult to perform |

## RINSE SOLUTION SAMPLING

| Advantages | Disadvantages |
|---|---|
| 1. Is appropriate for areas with non-accessible surfaces | 1. "Averages out" contaminants found in concentrated areas |
| 2. Produces rapid results | 2. Is impossible to identify where the contaminant was located |
| 3. Fewer samples are required | 3. Volumes may vary |
| 4. The samples require less run time | 4. And may require re-concentration or solvent extraction |
| 5. Is a simple method | |
| 6. Allows sampling without disassembling equipment | |
| 7. Is relatively non-invasive | |
| 8. Is not technique dependent | |
| 9. Is adaptable to on-line monitoring | |
| 10. And is applicable to many residues | |

## IN-PROCESS MONITORING

| Advantages | Disadvantages |
|---|---|
| 1. Would be rapid and economical | 1. Is an invasive technique |
| 2. Is useful for screening studies, production monitoring, process development, and initial validation | 2. Validation may be difficult |
| | 3. May be considered subjective |
| | 4. Is not quantitative |
| | 5. Many techniques are not fully developed |
| | 6. "Hot spots" and "critical sites" may be difficult to inspect |

If you are interested in our *Collecting Samples and Establishing Limits for Cleaning Validation* (PHA54), which helps learners recognize the need for established limits of cleanliness in cleaning validation, please contact your Account Director, or Pat Thunell at pat.thunell@ul.com.

# PREPARING FOR AN EU INSPECTION: KNOWING THE TERMINOLOGY

The terminology and responsibilities referenced in the EU directives may be different from those referenced by FDA and other regulators. Below are definitions of specific EU terminology that you can share with your GMP and manufacturing teams.

**Competent Authority**

- Each member state is required to identify a Competent Authority, which is the body in that state responsible for ensuring compliance with the EU's requirements and standards for medicinal products. For example in the UK, the Competent Authority is the Medicines and Healthcare Products Regulatory Agency known as the MHRA. In Denmark, it is the Danish Medicines Agency. The Competent Authority is responsible for performing inspections in its own member state.

**Marketing Authorization**

- Before a medicinal product can be supplied to member states, the supplier must first receive a marketing authorization. This can be granted only after detailed evaluation of all the scientific data on the safety and efficacy of the product. The evaluation is performed through the European Medicines Agency or by a member state's competent authority. Medicinal products imported from non-EU countries also require marketing authorizations.

**Manufacturing Authorization**

- A product that has received a marketing authorization cannot be supplied within the EU unless the location at which it has been manufactured has been granted a manufacturing authorization. This is obtained only if the location is regularly inspected by the competent authority in the member state concerned.

**European Medicines Agency**

- In addition to other responsibilities, the European Medicines Agency has a coordinating role for GMP inspections of manufacturing sites proposed in applications for marketing authorization. This coordination role is performed by the Inspections Sector within the agency.

**Site Master File**

- This is a document specified in the EU GMP guide. It should be created by the manufacturer and is submitted to the Competent Authority. It provides information on manufacturing operations and their control. It is used by an inspector prior to a regulatory inspection as an introduction to the manufacturer and its activities.
- Examples of the details required in the document include the quality management system, range of products manufactured, premises and equipment -- including drawings and plans -- organizational charts, release procedures, complaints system, process validation, quality control, distribution and self-inspection.
- It should be current and part of the manufacturer's GMP documentation system.

**Qualified Person**

- Within the EU, a Qualified Person (QP) must certify the release of medicinal products to the market. QPs have legal responsibilities and duties defined within EU legislation. They must be highly trained, professional people experienced in all the activities relevant to assuring the quality of medicinal products produced by their companies. In this issue, we discuss the Qualified Person requirement around batch certification.

EduQuest has written a course titled, ***EU Directives and Inspection Readiness*** (PHDV96), which is available today to our GMP subscribers.

If you are interested in learning more about this course, please contact your Account Director, or email Pat.Thunell@UL.com.

# EU'S QUALIFIED PERSON REQUIREMENT: BATCH CERTIFICATION

As many clients know, EduQuest (www.eduquest.net) is a leading regulatory consulting firm made up of ex-FDA officials, and members of their team author some of our key GMP courses. With our focus on EU topics in 2015, EduQuest has authored a new course on the Qualified Person (QP), scheduled to be released in Q3 2015 for all of our GMP Library subscribers.

The QP is an EU legal requirement, in which an individual is defined in a life science manufacturer for being responsible for certifying the quality of each batch of medicinal products before it is released for distribution to the market. The QP is also responsible for the system that monitors and responds to adverse reactions identified in medicinal products supplied to the market. The QP role was first established in 1975 and is important within EU legislation; it is unique to EU member states.

This article focuses on the role of the QP as it relates to batch certification, which is also a key chapter in the course.

## Manufacturing Authorization

A product that has received a marketing authorization cannot be supplied within the EU unless the location at which it has been manufactured has been granted a manufacturing authorization. This is only obtained if the site is regularly inspected by the Competent Authority in the member state concerned.

Each holder of an authorization to manufacture medicinal products must name a person or a number of people who are eligible to act in the capacity of a QP. A manufacturing authorization is also required to produce clinical trial material; this authorization is also required to name a person or a number of people to act in the capacity of a QP.

## QP Requirements

These are the requirements in order for a person to operate as a QP for batch certification:

**Legal basis**: The role of the QP is broad and has significant responsibilities which are defined in EU law. The role can only be performed by individuals with the correct educational background and experience. EU Directive 2001/83 defines the requirements for eligibility; these requirements are stringent and legally binding. Each member state must ensure that QPs in their country fulfill the minimum conditions defined in this Directive.

**Qualifications required**: The EU Directive gives considerable detail on the formal qualifications that a QP should have. For example, the QP must have followed at least a 3-4 year university course in a scientific subject that is relevant to pharmaceutical industry such as pharmacy, chemistry, biology and medicine.

# EU'S QUALIFIED PERSON REQUIREMEN T: BATCH CERTIFICATION *(Continued)*

**Experience required**: The QP is also required to have obtained the necessary practical experience over at least two years with one or more authorized manufacturers of medicinal products. They should have gained experience in qualitative analysis of both medicinal products and active ingredients; in addition, the QP should be experienced in all the testing and checks required ensuring the quality of medicinal products.

**Assessment of QPs**: A QP must be formally approved by a member state's own mechanism before the individual can be named as a QP on a manufacturing authorization. Each member state, through their Competent Authority, has defined mechanisms to ensure QPs satisfy EU requirements. For example, the Competent Authority in Denmark, the Danish Medicines Agency, performs the assessments on individuals who wish to operate as a QP.

**Maintaining knowledge**: Once in position, QPs have a personal and professional duty to keep their knowledge and experience up-to-date. It is expected that this would cover:

- pharmaceutical quality management,
- regulatory changes , GMP guidelines,
- product manufacturing and control technology, and general work practices.

**QP change in role**: In the event of a QP making a major change in job responsibilities, the QP and the senior management of the company involved should recognize the need for additional education and training and take all the necessary actions to ensure this takes place. Such extra training should be undertaken before the QP acts in a new situation. It may also be necessary for the competent authority to be notified and renewed authorization to operate as a QP obtained. QPs have a professional duty to decline to act as a QP in the certification of product types for which they do not have the relevant experience and knowledge.

**Transitional arrangements**: EU regulations defined transitional arrangements to assist companies and member states in introducing the role of the QP. These state that if an individual gained the required scientific qualifications before May 1975, and gained relevant experience in production, analysis, testing and checking before May 1985, they are allowed to operate as a QP.

## The QP Role in Batch Certification

Certification by one person: a fundamental requirement that all manufacturers of medicinal products must observe if they supply product to the EU or export products from the EU:

Each batch of finished product must be certified by a QP within the EU before being released for distribution.

Before a batch can be released, the QP must sign a register or equivalent document as a record that they have carried out a proper evaluation. This also means that if a product defect needs to be investigated or batch recalled, the QP who certified the batch is readily identifiable.

**Routine duties of a QP**: Before a batch can be certified, the QP must ensure that at least all the following requirements have been met:

- The batch and its manufacture comply with the information included in the marketing authorization submitted for the product;
- Manufacture has been carried out according to the EU GMP Guidelines;
- If a batch of product has been imported from a non-EU country, the QP must be able to confirm that it was manufactured in accordance with GMP standards that were at least equivalent to those of the EU;
- The principle manufacturing and testing processes have been validated;
- Account has been taken of the actual production conditions for the batch and the manufacturing records;
- Any deviations or planned changes in production and quality control were authorized by the persons defined as responsible in the local quality assurance system;

# EU'S QUALIFIED PERSON REQUIREMENT: BATCH CERTIFICATION *(Continued)*

- Any changes that require variations to the marketing or manufacturing authorization have been notified to and approved by the relevant authority;
- All necessary checks and tests have been performed;
- Any additional sampling, inspection, tests or checks have been carried out if these were required because of deviations or planned changes;
- All production and quality control documentation has been completed and signed by the staff authorized to do this;
- All the necessary internal audits and external audits of suppliers have been carried out according to the local quality assurance system;
- Based on the QP's knowledge of the manufacturing process, all factors relevant to the quality of the batch have been taken into account.

## How the QP Works with Other Personnel

**QC Department**: The role of the QP does not remove responsibility from the QC department and the head of QC. The QC department still has line management responsible for key activities such as sampling, specifications, testing, batch documentation review, assessment of deviations, reference samples and assuring that products are not released for sale until their quality has been judged to be satisfactory.

The EU GMP Guidelines have the same requirements as the QC department and as the US FDA and most other regulatory authorities around the world.

**Colleagues**: In considering how the QP performs their routine duties and obtains the information to certify a batch, the size and complexity of the operation must be taken into account. If the QP is working in a small simple operation with a limited range of products, it is much easier to obtain all the information required and the QP can take direct responsibility for doing most of the checks required.

**Active Pharmaceutical Ingredients (API)**: While APIs do not need to be certified by a QP, the QP is responsible for certifying that the finished medicinal product that was used with the API was manufactured in accordance to EU GMP requirements and to the required specification. This will usually require the QP to ensure that regular audits are performed on the API supplier.

**QP codes of practice**: A number of codes of practice have been prepared by member states and professional organizations, such as the UK's competent authority, the MHRA, and the European Industrial Pharmacists Group. These codes provide operational guidelines for carrying out the functions of the QP; they also include professional codes of conduct.

A QP who fails to meet their obligations will be subject to disciplinary procedures usually administered by the Competent Authority in the member state. This could include deletion of the QP's name from the manufacturing authorization. The codes of practice provide additional information on the subject found in the EU Directive and EU GMP Guidelines. The codes exist to assist the QP, their employers and the competent authorities.

In the next issue of the Communiqué, we will discuss the QP role in more complex "supply" situations, including importation from outside the EU and mutual recognition agreements.

# OUR NEW QP COURSE


## About:

Our new QP course examines the role of the Qualified Person (QP) as defined in European Union legislation. The role impacts three important areas: release of medicinal products to the market, release of clinical trial materials and pharmacovigilance. Each of these subjects is addressed as well as the legal background to the role and the qualifications and experience required to become a QP. The course references several EU regulations:

- EU Directive 2001/83/EC, Code Relating to Medicinal Products for Human use
- EU Guide to Good Manufacturing Practice, Annex 16, Certification by a Qualified Person and Batch Release
- EU Directive 2001/20/EC, Clinical Trials
- EU Guide to Good Manufacturing Practice, Annex 13, Manufacture of Investigational Medicinal Products
- Rules Governing Medicinal Products in the European Union, Guidelines on Pharmacovigilance for Medicinal Products, Volume 9A
- Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007, Chapter 3, UK Guidance on Manufacture, Code of Practice for Qualified Persons in the Pharmaceutical industry. Issued by the Medicines and Healthcare products Regulatory Agency in the UK

## About UL EduNeering

UL EduNeering is a business line within UL Life & Health's Business Unit. UL is a premier global independent safety science company that has championed progress for 120 years. Its more than 10,000 professionals are guided by the UL mission to promote safe working and living environments for all people.

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.