SampleQ

Automated swab sample testing

- APPLICATION NOTE -

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1. Situation

During pharmaceutical manufacturing extended cleaning measures are taken to make sure that production equipment is not a source of cross contamination between different drug batches. All residues of active pharmaceutical ingredients have to be removed to ensure that the quality of the manufactured product is not compromised by waste from previous manufacturing activities. Post production cleaning will in turn prevent issues with the following drug products.

Verification of the effectiveness of the cleaning processes is of the essence. Therefore, Good Manufacturing Processes (GMP) do not only include strict cleaning procedures, but involve extended sampling and chemical analyses to prove acceptancy criteria are met.

As part of the GMP regulations in force, this cleaning validation is performed by taking a swab sample of the production equipment, followed by extraction of the swab in product-specific solvents. The subsequent liquid chromatographic analysis and data processing are already highly automated, but sample extraction is still performed manually. In order to eliminate this bottleneck SampleQ was contacted to replace this labor intensive step by an automated extraction solution. In addition to increased workflow and more reproducible results, the risk of human errors and harmful solvent exposure during the liquid extraction process is greatly reduced.

2. SampleQ

Since the establishment of Interscience more than 35 years ago, an impressive amount of knowledge and practical experience has been built up in the design and implementation of automated chromatography systems. These are used in both routine and R&D laboratories in the form of standalone systems or set-ups that are fully integrated with the analytical high-tech instrumentation (GC, (U)HPLC, MS). The field of application of these total solutions is very broad, ranging from pharmaceutical screening and metabolomics through to environmental analyses and clinical chemistry.

SampleQ is firmly based on this expertise and develops, tests and integrates sample preparation systems for analytical laboratories. Our modern intelligent solutions are based on modular platforms that are widely recognised as world-leading in the laboratory world. Thanks to our expert instrument makers, we have the capacity to develop custom-made solutions in case your application requirements exceed the possibilities of the standard available modules. For complete integration into your total solution, we are able to write the necessary software add-ons. Our approach is pragmatic while our solutions are efficient, elegant and relevant.

3. SampleQ's activities

In recent years there has been increasing pressure on analytical laboratories. Economic realities threaten the existence of analytical departments and are expressed in terms of cost per sample, solvent management and overall laboratory efficiency. The increasing pressure to do "more with less", not only results in a redistribution of tasks within the lab, it also slows down the accumulation of expertise and threatens the future development and evaluation of new techniques, methods and instrumentation. Good ideas for automation may be around, but due to a constant lack of time they remain in the concept phase and are not tested against the needs and requirements of everyday practice.

However, automation is more than simply increasing analytical throughput. We regularly find, for example, that the introduction of new standards translates into more than just higher quality requirements. The new, stricter targets in terms of detection limits, accuracy, repeatability and reproducibility suddenly come into conflict with the variation inherent in the established manual preparation of samples.

SampleQ recognises these trends and offers a wide range of solutions and services to assist you in optimising your laboratory processes. Central to our approach are increasing general efficiency and throughput while at the same time reducing operational costs.

Our services are tailored to your sample preparation needs and include:

- Feasibility studies
- Process analysis
- Workflow improvement
- System integration
- Advice & consultancy
- Validation & certification
- Data mining

For more detailed information on our activities, please visit http://www.sampleq.com/.

4. The Q approach

4.1 Genuine laboratory automation

All too often, automatic sample preparation is interpreted far too narrowly. Many of our competitors often see a simple conversion from a particular manual operation to a glorified autosampler as a massive success. Nothing could be further from the truth. A broader, far-reaching approach is needed to face up to the more demanding challenges. We consider the entire analytical procedure, from "prep to rep", as an integral part of our automation solution. Existing manual procedures should not be copied blindly in the automation process. Are equivalent alternative separation technologies available that allow a more effective automation? How do you convert the typical serial approach of manual sample preparation to the parallel sample processing logic of the world of automation? It is clear that a one-to-one translation is inadequate because true laboratory automation is characterised by intelligent sample preparation with an eye for cost and quality.

4.2 Our approach in practice

What specific approach does SampleQ take to achieve this intelligent laboratory automation while taking into account lean and six-sigma? Our strategy is clear, well thought out and flexible where needed. It consists of four essential steps: a preliminary study, a feasibility assessment, implementation and, finally, the validation of your automation solution.

5. The Swabbing procedure

A suitable extractable solvent is used to release the residues from the swab head. Depending on the particular SOP in each area, this swab sample may need to be filtered and/or sonicated to extract the residues as completely as possible. These sample prep procedures place a heavy premium on the intrinsic quality of the materials used in the swab head and the filters. The use of anything less than the highest quality of suitable pre-treated polyester swabs can prove to be a source of extraneous contamination in the subsequent assay.

The method development and validation steps are often conducted on test coupons to serve as examples of the equipment or surfaces to be cleaned. The choice of filter and solvent used in sample preparation is also critical since they can have an impact on the recovery, influence extractable, and efficiency of filtration. Several publications have reported a systematic study of a variety of solvent conditions and pH and their impact on the percent recovery and efficiency of filtration. While it may be intuitive to choose the solvent conditions used in the subsequent analysis (e.g. HPLC) as the extractable solvent, this may sometimes compromise the filtering efficiency and the percent recovery. In addition, analytical considerations play an important role in the cleaning validation as well.

6. Analysis of residues – Analytical considerations

The purpose of swab sampling as part of a cleaning validation protocol is to be able to prove that the cleaning process served its purpose. That purpose (cleaning the surfaces to avoid any cross-contamination) is best measured in the validation step as a percent recovery of seeded residue. Such a measurement provides an estimate of Residue Acceptable Limit (RAL). The measurement of percent recovery is accomplished through an analytical test, typically either HPLC (High Performance Liquid Chromatography) or TOC (Total Organic Carbon).

HPLC-UV systems commonly carry additional detectors such as mass spectrometry (MS - for specificity and identification). It is important to realize early in the method development process for cleaning validation that percent recovery will be directly influenced by the interaction of the particular assay detector with each of the variables involved in the protocol. It is best to conduct a pre-study of the influence of the various factors involved in the cleaning in order to ensure that their effect on the final percent recovery measurement is well understood. It is typically very cumbersome to deconvolute an aberrant percent recovery result 'after-the-fact' for a method that may have been in use over a long period of time. Cleaning Validation is a complex activity requiring a careful choice of sampling procedure and analytical method. It is therefore highly recommended to always use only the

highest quality materials for swabs, filters, and solvents in cleaning validation protocols in order to assure that they cannot serve as sources of aberrant results, if and when those results do occur.

Both HPLC and TOC are highly sensitive methods that serve as assays for cleaning validation protocols. HPLC by its very nature is a specific assay in that it can identify peaks and assign them to specific residues, while TOC is a classically non-specific measure of overall carbon burden in a given environment.

Since these assays are both quantitative, typical analytical parameters such as accuracy, precision, linearity, detection, and quantitation limits must be evaluated as part of method development. While HPLC is a very commonly used tool in the pharmaceutical industry, the complexity, trace level sensitivity, and criticality of the cleaning validation protocol to drug safety merits special attention to the results from HPLC analysis. It is important to avoid using materials that might serve as sources of contamination through interference with the UV spectrum, or the detector of choice. In the event that such interference in the assay is unavoidable, understanding and perhaps even quantitating the interference so that the cleaning validation protocol is appropriately "science based" would pass muster under an investigation.

Attempts should be made to identify any additional peaks that appear in the chromatograms of swab extracted samples besides those arising from the expected residues. TOC (Total Organic Carbon) is a conductometric assay that correlates with carbon concentration, which provides an overall, non-specific estimate of residue burden left behind on the surface from a previous batch run. TOC measurements are highly sensitive and typically reported at the part per billion (ppb, or µg/L) level. As such, great care must be taken during the swab sampling and sample preparation to minimize external sources of organic carbon contamination.

7. Our modus operandi

7.1 Required hardware & software

Based on the currently SOP, the required hardware and software is summarised as follows:

- Fully automated swab sample preparation module with a **total length of 85 cm**
- Sample rack for **100 mL bottles**

- User selectable pre-programmed solvent addition
- Choice of 5 different extraction solvents (1 L bottles)
- Volume range: from 10 to 50 mL

- User selectable pre-programmed extraction time
- Time range: from 5 to 15 minutes

- Samples are automatically transferred to **HPLC / UPLC vials**
- Vial trays are compatible with existing HPLC/UPLC instrumentation, eliminating error-prone process of manually transferring the vials to the LC autosampler trays
- Dual wash station for thorough needle & syringe cleaning (strong & weak solvent)
- Desktop computer with 19" flat screen, Windows7 professional
- Remote-control software (incl. scheduling)
- Technical installation & hardware programming

7.2 Summary

Cleaning validation is an essential step in the critical cleaning of pharmaceutical manufacturing environments. Swabbing is the preferred method of sampling such surfaces in the process of cleaning validation. The sampling and analysis methods have a direct and measurable impact on the percent recovery results from either HPLC or TOC assays. It is critical to ensure that the swab, filters, and associated materials used during the process are of the highest possible quality and do not contribute even trace levels of impurities that can interfere with the results.

7.3 Validation / delivery

On delivery, SampleQ provides turnkey software templates for the automated steps of the Swab sample test procedure (programming) and verifies the technical operation (communication & alignment) of the installation.

A full analytical and operational validation of the automated steps of the Swab sample test procedure is not included on delivery but can be carried out according to your production specific quality requirements at additional charges.