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Cleaning Validation for Medical Devices Exposed to a Large Number of Processing Agents

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INTRODUCTION

Medical devices are exposed to a wide range of processing agents and materials during manufacturing. Depending upon the medical device, residual levels of these processing agents and materials pose a potential toxicological risk to patients. Manufacturers of medical devices need to identify and properly control for contamination of the medical device from processing agents and materials encountered during the manufacturing of the device. This is done by validation of the cleaning of the medical device.

For the validation of the cleaning of a medical device, a cleaning limit needs to be established for each residual processing agent. The cleaning limit is the level below which the residual processing agents pose no risk to the patient. Traditionally this is done by performing a toxicological assessment following ISO 10993-12 on each individual processing agent (and each component of a processing agent if it is a mixture) and setting a cleaning limit for each chemical. When the total number of possible chemicals from the processing agents is small (less than 10) and all have toxicological data available, this is the preferred approach. Unfortunately, this is commonly not the case. If the manufacturer is faced with a large number of potential chemical residues from the processing agents (greater than 10), the time and cost of a complete toxicological assessment to set the cleaning limit of each component may be prohibitive. Also, complete toxicological data may not be available in the literature which could prevent the determination of the cleaning limit for a specific compound.

We propose an approach to assist medical device manufacturers when faced with the challenging task of setting cleaning limits for a large number of potential contaminants from process agents or when complete toxicological data is not available. Our approach is to set a worst case scenario cleaning limit and then test the medical device by a battery of sensitive analytical techniques to determine which of the potential contaminants are actually present on the device at a level that could potentially present a risk to the patient and eliminating from further evaluation any contaminants that are present at levels that present no risk to the patient.

REGULATORY REQUIREMENTS

The Quality System Regulations from the US FDA capture the requirement for medical device manufacturers to validate the cleaning of the medical device by stating that each manufacturer shall (1,2):

Establish and maintain procedures to prevent contamination of product by substances that could be expected to have an adverse effect on product quality.

Establish and maintain procedures for the use and removal of manufacturing materials to ensure that it is removed or limited to an amount that does not adversely affect the device's quality.

As should be obvious, any residual processing agent that presents a toxicological risk to the patient would adversely affect the quality of the device.

In addition to the FDA QSR, ISO 13485 requires the establishment of documented cleaning specifications for a medical device if the any of the following apply (3):

- *Product is cleaned by the organization prior to sterilization and/or its use, or*
- *Product is supplied non-sterile to be subjected to a cleaning process prior to sterilization and/or its use, or*
- *Product is supplied to be used non-sterile and its cleanliness is of significance in use, or*
- *Process agents are to be removed from product during manufacture.*

As can be seen, both sets of regulations require cleaning validation for certain types of medical devices and manufacturing practices.

REVIEW PROCESS FLOW TO IDENTIFY THE MANUFACTURING MATERIALS

Before starting cleaning validation, the manufacturer needs to identify all of the manufacturing materials and processing agents that contact the medical device. This is done by evaluating the complete manufacturing process from beginning to finished product.

Manufacturing materials and processing agents can be broadly categorized into the following groups:

- Organic residuals. Examples: lubricants, detergents and disinfectants.
- Inorganic residuals. Examples: metals and metal ions.
- Particulates. Examples: Metallic particles from a cutting process.

The end result of the process review should be a complete list of all possible contaminants that could be on the device.

The manufacturer can perform a risk analysis to determine the likelihood of each processing agent remaining as a residue on the medical device. For example, consider the following hypothetical process. A medical device is exposed to chemical A in the first step of the manufacturing process and chemical Z is introduced in the last step. After the medical device is exposed to chemical A, the medical device undergoes 3 steps in the manufacturing process that are likely to wash off chemical A before the device is exposed to chemical Z. Therefore, chemical Z is much more likely to remain as a residual than chemical A. In this case, the manufacturer could use this risk assessment to focus more on chemical Z during the cleaning validation following proper documentation of the risk assessment.

DETERMINATION OF WORSE CASE SCENARIO CLEANING LIMITS

After the potential hazardous contaminants from the manufacturing process have been identified during the risk assessment, the acceptable level for the contaminants is determined. Ideally, a toxicological assessment should be done for each potential contaminant. However, if a large number of potential contaminants have been identified, the time and cost of a complete toxicological assessment may be prohibitive. In this case, the determination of a worst case scenario cleaning limit is recommended.

To determine a worst case scenario cleaning limit, a level needs to be determined below which even the most toxic contaminants would not present a risk to the patient. Unfortunately the Quality System Regulations and guidances from the US FDA do not provide any assistance in evaluating the toxicological risk of contaminants on a medical device. However, guidelines from the pharmaceutical industry do pertain to establishing thresholds for patient exposure and can be applied to this situation.

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has issued a guideline titled “Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk” (M7). The ICH M7 guideline describes a consistent approach to identify, categorize, and control DNA reactive and mutagenic impurities taken in by patients to limit the carcinogenic risk. In ICH M7 can be found the Threshold of Toxicological Concern defined as follows (4):

“A Threshold of Toxicological Concern (TTC) concept was developed to define an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects”.

The TTC (expressed as µg/day) represents the level below which intake of a potential compound would not present a significant carcinogenic risk to a patient. In ICH M7, the guidance also accounts for acceptable higher daily intakes for shorter exposure periods. The recommended TTC by duration of treatment from the ICH M7 guideline are as follows (4):

Acceptable Intakes for an Individual Impurity

Duration of treatment	*? 1 month*	*>1 – 12 months*	*>1 – 10 years*	*>10 years to lifetime*
Daily Intake (ug/day)	*120*	*20*	*10*	*1.5*

These acceptable intake levels are based upon exposure and are determined for mutagenic compounds. Mutagenic compounds represent the worst case scenario for toxicity; therefore any compound below these levels for the listed duration of treatment would present no toxicological risk.

Although these recommendations were developed for pharmaceuticals, the acceptable daily intakes are only based upon toxicity and the daily intake by the patient. Therefore a manufacturer of a medical device could use these levels based upon the intended exposure of the patient to the medical device.

The TTC could then be used to calculate a worst case scenario cleaning limit (CLwc) for all individual potential contaminants as follows:

CLwc =TCC (ug/day)×(elution time (day))/(# of devices)

where elution time is the time required for 100% of the individual potential contaminant to elute from the device into the patient and the number of devices is the expected total number of devices used on the patient. Since the elution time is most likely unknown, the worst case scenario would be for entire amount of the potential contaminant to enter the patient on first exposure, so 1 day is used as the elution time for the CLwc. If the number of devices is variable, a realistic estimate of the largest number of devices is used. The final units for the CLwc are µg /device. Instead of the number of devices, an amount of device (i.e. weight, surface area, length, etc.) can also be used.

Once the CLwc had been calculated, the medical device can be tested for residual process contaminants from the manufacturing process.

ANALYTICAL TESTING FOR RESIDUAL PROCESSING AGENTS

An analytical testing strategy needs to be developed that will detect all of the processing agents identified in the risk assessment of the manufacturing process. While the analytical testing strategy will need to be specific to the manufacturing process and the medical device, each analytical testing strategy will include the following steps: Washing the residues from the medical device, testing the washes for the processing agents, evaluating the results against the CLwc, and setting compound specific cleaning limits.

1 . Washing the medical device

The first step is to wash the medical device in solvents that are expected to dissolve the processing agent. The residual processing agents are likely to have varying polarities, therefore more than one solvent will probably be needed. Usually water and an alcohol such as isopropanol will be sufficient but other solvents may be appropriate based upon the expected residual processing agents. The solvents selected and the conditions should be appropriate for the purpose of washing contaminants from the surface without being so aggressive as to dissolve or cause leaching from the medical device.

2. Analysis for Residual Processing Agents

The washes are then analyzed for the residual processing agents. The analytical methods will be selected based upon the residual processing agents with the following analytical methods being commonly used:

1. Headspace GC-MS for volatile organic residual contaminants
2. Direct Inject GC-MS for semi-volatile organic residual contaminants
3. LC-UV/MS for non-volatile residual organic contaminants
4. ICP-MS for inorganic residual contaminants

3. Evaluation of Results

At the end of the analytical analyses, the level of each residual processing agent is evaluated against the CLwc with the following potential outcomes:

The level of the residual processing agent is below the CLwc. The residual processing agent would not present a risk to the patient and therefore the device would be considered clean from this processing agent.

The level of the residual processing agent is at or above CLwc. The residual processing agent should be submitted for a toxicological evaluation to set a compound specific cleaning limit as described in the next section.

4. Determine Compound Specific Cleaning Limit

The manufacturer should follow ISO 10993-17 to set the cleaning limits for each processing agent above the CLwc. When limited toxicological data is available, at a minimum the LD50 values (readily obtained from the MSDS) can be used to calculate the compound specific cleaning limit.

The compound specific cleaning limit will likely be higher than the CLwc. If the level of the residual processing agent observed from the analytical analyses is below the compound specific cleaning limit, the device would be considered clean from residual for the processing agent. If the level of the residual processing agent is above the compound specific cleaning limit, the device would not be clean from that processing agent.

CONCLUSION

Manufacturers of medical devices are required to demonstrate that their medical devices do not present a threat to patient health from residual processing agents. An experimental strategy was presented that allows the manufacturer to test for all of the potential residual processing agents on the medical device based upon the determination of a worst case scenario cleaning limit. For medical devices where there is a risk of a large number of residual processing agents, the manufacturer may find this approach to be more efficient and less costly than determining the cleaning limit for each compound from a toxicological assessment.

REFERENCES

1. Code of Federal Regulations, Title 21, Quality System Regulations, Part 820.70(e), 2013
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3. ISO 13485:2003, Medical devices -- Quality management systems -- Requirements for regulatory purposes, section 7.5.1.2.1.
4. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline titled “Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk” (M7) 31 March 2017

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