General Discussion

This document describes the rationale and recommended microbiological methodology for consideration during cleaning validation of product contact surfaces for Active Pharmaceutical Ingredients (APIs) and drug products.

The guidance on Clean Equipment Hold Time may be used to determine if micro testing is required during cleaning validation.

Microbial control should be taken into consideration for cleaning procedures that provide conditions favourable to the growth of microorganisms. If the risk of the growth of microorganisms is high, microbiological sampling of product contact surfaces is one activity that can demonstrate that the cleaning process does not contribute to the increase of the microbial load above previously defined acceptable levels.

Microbiological cleaning validation for product contact surfaces for drug products and the final stage of drug substances is advisable when the surfaces are not sterilized and water is used as a final rinse. Water used to clean and rinse equipment is capable of supporting growth and can potentially add bioburden. When it is determined that there is a microbial risk due to the cleaning procedure, it is important to demonstrate that the cleaning process does not create an adverse effect on the drug substance and product.

When cleaning validation microbiological sampling is required, a final purified water (PW) or water-for-injection (WFI) rinse sample of product contact surfaces following the cleaning procedure is the preferred sample collection method. Alternatively, if a water rinse sample is not practical, then direct sampling (e.g. contact plates or swabbing) of the product contact surfaces may be used.

Regulatory Requirements

The FDA states in 21 CFR 211.113 that “Appropriate written procedures designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed”. In addition, the FDA Guide to Inspection of Validation of Cleaning Processes (1993) states, “Microbiological aspects of equipment cleaning should be considered. There should be some evidence that routine cleaning and storage does not allow microbial proliferation”.

The PhRMA report on microbiological monitoring in nonsterile pharmaceutical manufacturing areas (1997) recommended that depending on the product type, cleaning validation should include microbial sampling to ensure microbiological quality.

The ICH Q7A Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients states “Equipment cleaning/sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).

