

## 19. APPLICATION OF VALIDATION PRINCIPLES TO OTHER ANALYTICAL TECHNIQUES

### 19.1. Cleaning Method

To discuss cleaning validation in detail is beyond the scope of this work, as this has become an independent field. However, important steps required for cleaning validation will be briefly described. Readers are encouraged to research relevant publications on this subject. Recently, Kirsch has published an excellent review article on this subject (48). Cleaning validation is a regulatory requirement. The FDA has published a document titled "Guide to Inspections, Validation of Cleaning Processes" on this subject for field application. It is common industry practice to use the same equipment for production of a variety of products. The FDA has placed an increased emphasis on the cleanliness of the equipment to eliminate or minimize the risk of cross-contamination and adulteration of drug products.

Several analytical methods have been used by the pharmaceutical industry to demonstrate the cleanliness of process equipment surfaces. For low-level residues in rinse samples, the electronic conductivity technique are used. This technique is applicable to samples such as detergents and cleaning agents, which contain one or more ionic species. However, this technique is nonspecific and cannot be applied to neutral or highly polar compounds. Also, the FDA has specified a requirement that a correlation must be established between measurable conductance and concentration around the cleaning limit, which is a time-consuming process and not always possible for all analytes in a given formulation.

UV-visible spectrophotometry is another approach used for the detection of residue in rinse samples. This technique is sensitive but is dependent on the presence of a strong chromophore in the analyte for trace level determination. This is also a nonselective technique and not discriminating if more than one UV-active analytes are present in same sample.

Total organic carbon (TOC) has gained wide acceptance for cleaning applications (33,48). This technique is highly sensitive and specific for organic carbon-bearing analytes. TOC may be used in tandem along with conductivity, pH, and perhaps titrimetry to demonstrate the absence of both acid and alkaline detergents used for cleaning. TOC is only applicable to aqueous samples, and extra caution is required during sample acquisition and preparation to avoid bias in results due to carbon contamination.

High performance liquid chromatography (HPLC) has successfully been applied for cleaning residue samples. HPLC is sensitive for many pharmaceutical actives, and the necessary specificity can be obtained by this technique. For this technique, there are a variety of detection modes, such as spectrophotometric, electrochemical, fluorescence, and refractive index, to handle the diversity of pharmaceutical compounds.

Before the validation process begins, the appropriate predetermined level of cleanliness, i.e., at or below the limit at which equipment is considered clean, the final solvent used for the cleaning of equipment, and the type of swabs to be used should be chosen in consultation with the manufacturing group. It is critical that the limit agreed upon is practical and routinely achievable when an appropriate cleaning assay method is followed. Additionally, an acceptance limit that assures