Hot Spot

A surface that is judged to be hard to clean or has the potential for hold up of materials.

Maximum Daily Dose (MDD)

The maximum dose of active substance (usually mg or g) typically administered to a patient in any 24hr period (e.g. as referenced in the Core Data Sheet).

Minimal Effect Dose (MED)

The minimum dose at which there is an observable pharmacological effect in man. Note: The MED is expressed as a weight of active substance (usually mg or g) per day.

Minimum Therapeutic Dose (MTD)

The minimum amount of active substance (usually mg or g) typically given to a patient on each occasion as referenced in the Core Data Sheet.

Mobile Equipment

Items of product contact equipment that are routinely disconnected and reconnected to plant to enable processing steps as part of an equipment train. This excludes small, easily inspected or disposable items and spares (e.g. sight glasses, small flexible lines, filter bags etc).

Multi-purpose Equipment/Plant

Non-dedicated plant or equipment used for the production of more than one intermediate or API where the potential for cross-contamination exists.

Nil Effect Dose (NED)

Based on human data, is the maximum (single or repeated) dose at which there are no observable pharmacological effects in man.
Note: The NED is expressed as a weight of active substance (usually mg or g) per day.

No Observable Effect Level (NOEL)

The dose level (usually mg or g) at which no toxicological effects are observed.

Risk Assessment Factor

A factor used when defining an acceptance limit. It is used during calculation of acceptance limits to ensure that the level of contamination is sufficiently low from a pharmacological and toxicological standpoint.

Stain

A mark (e.g. surface marking/etching/discoloration) which has appeared since the installation of new plant or equipment will be considered a stain if both physical and chemical documented procedures fail to remove it.

Trial Cleaning

Cleaning carried out prior to the use of the plant/equipment for manufacture to establish the use of clean in place devices, potential hot spots or high level

- The operations related to interval cleaning may be organized into their own cleaning instructions or it may be beneficial to incorporate interval cleaning activities into processing instructions (e.g., a post processing rinse).

- If a cleaning agent is used that is not shared by the manufacturing process, such as detergents or highly toxic solvents, the appropriate residual limit must be applied to the procedures acceptance criteria. (detergents must also have their removal validated).

2 (b). Visual Inspection of Dedicated Equipment – Cleaning Between Campaigns:

Dedicated equipment campaign cleaning refers to the cleaning process performed between the end of one product campaign and the start of the next campaign of the same product. This section of the procedure addresses those cases where there is known to be a potential quality concern with
carryover of amounts of material (e.g. degradation products) in excess of a specific RAL.

Consideration of the following is suggested as part of the development of an end of campaign cleaning methodology:

- For those products where the visually quantifiable amount is known, or is believed to be within a range referenced in literature sources1,2 , and is below the established RAL; standards may be developed that allow some amount of visible residue. The visual standard should be well defined, and training of inspectors on how to subjectively determine
pass/fail results should be documented. Otherwise;

- The minimum requirement is visually free of residues.
- For large closed systems, if the only acceptance criterion for release of equipment back to the production of product is visual inspection; and if the cleaning evaluation activity determines that there is a potential quality concern of carryover of excessive amounts of material (e.g. due to degradation products), areas that are difficult to clean may require more emphasis during the cleaning process. These areas would be characterized as difficult to clean, with disassembly as necessary, and would provide evidence of cleanliness beyond viewing the vessel interior through a sight glass or a man-way with the use of a mirror and
flashlight.

It should be noted that the validation of cleaning procedures with respect to the active ingredient for dedicated equipment does not require. The resource required to perform equipment disassembly on a routine basis, however, may justify the performance of a study to “validate” that the hard to clean areas are visibly clean for a number of consecutive cleanings as evidence that the visual inspection can be relaxed for subsequent cleaning. This approach is appropriate for the same reasons that swabbing provides additional assurance of cleanliness during validation but may be discontinued after a given number of successful cleanings.

3. Routine Visual Inspection of Multi-Purpose Equipment.
For routine visual inspection of multi-purpose equipment, or those inspections that occur as the last visual check of a system prior to release back to production of the next product, consideration of the following is suggested as part of the development of a multi-purpose cleaning methodology:

- There will be a visual inspection and an analytical sampling method (if required) employed for verification of cleanliness.

