are trapped in difficult to clean areas not effectively cleaned by the CIP system (e.g., dome nozzles or dead-legs).

Consideration of the following is suggested as part of the development of a manual cleaning methodology:

- The inspection of major equipment following or during manual cleaning should take place prior to the analytical rinsing or swabbing to provide a greater probability that target residues are removed prior to sampling.
- The inspection should not substitute for the final visual inspection that would typically take place following analytical sampling. The final visual inspection determines the success or failure of the validation execution.

- For those areas that will be inspected again for final determination of visual cleanliness, this in-process inspection may be less stringent than the final visual inspection. For instance, flashlights and mirrors might not be necessary, complete absence of visible residues might not be required, and complete disassembly of equipment might not be justifiable. The justification for this approach being that this type of inspection is not the final inspection and once a residue has been acted upon in some manual manner (e.g., scrubbing, power washing) it is more likely to be effectively removed subsequently by the CIP system.

- The inspection is at the discretion of the process designer(s) and is not required. The purpose of inspection after manual cleaning is to measure the effectiveness of the manual methodology before resuming CIP cleaning. It might not be justified for example, if the manual methodology has been shown to be rugged in the past, or is simply a precautionary measure to provide a greater probability of passing acceptance criteria at the conclusion of the cleaning process.

Inspection of equipment that is cleaned manually and can be 100% visually inspected prior to release back to production (e.g., mills and minor equipment) is not the subject of this specific section. Rather, the inspection of these examples should follow the guidance of "final visual inspection" detailed below.

2 (a). Visual Inspection of Dedicated Equipment – Interval Cleaning:

Interval cleaning, or cleaning processes that take place within a campaign of the same product, are appropriate when an evaluation of the material being cleaned has been completed and there are no quality concerns (e.g. degradation of material) about carryover of some amount of one batch into the next batch.

Although the intent of this section of the procedure is focused primarily on dedicated equipment it may also be applied to interval cleaning that takes place between batches within a campaign using multi-purpose equipment.

difficult to clean (marker) compound or is the marker by default for a single product cleaning procedure. The routine cleaning procedure with any disassembly would be used in validation. Consideration of the following is suggested as part of the development of these types of visual inspection for validation:

- Those areas identified as difficult to clean by the cleaning evaluation exercise should be visually inspected with disassembly as necessary.

- The areas described above are often times swab sampled as part of the acceptance criteria of the cleaning validation protocol and they should be verified as visually clean prior to sampling, and any non-conformance reported as a cleaning failure.

- There might be some areas that are identified as requiring persistent manual intervention and inspection (i.e., where product hold-up is found and which are not addressed through a corrective action that changes the design of the equipment or the procedure). During the execution of the validation these areas should be included as a point of inspection. These areas should also be included in the routine visual inspection after validation to insure effective cleaning subsequent to the validation activity. These same areas may be included in the inspection following manual intervention during cleaning as the situation warrants, however, each of these hard to clean areas should be re-examined as part of the final visual inspection.

5. Visual Quantitation

If the only verification of cleaning changeover processes to be conducted on equipment is visual, then the visually detectable quantity must be known and documented.

An exception can be made for generally recognized as safe (GRAS) compounds.

a. Laboratory Studies

The study leading to the required documentation should be conducted using a standard methodology and conditions that limit variability. The method and conditions should be defined within an approved site procedure. The determination of visual quantitation in production equipment should be discouraged for the inherent safety, equipment integrity, and subjectivity considerations associated with such an approach. Laboratory studies typically include:

- The spiking of coupons of a known surface area that represent the materials of construction present within the system.

- The coupons are spiked at the swab RAL concentration and adjusted to be directly proportional to thesizeof the coupon.

- The coupons are then dried and examined under conditions designed to represent the actual manufacturing environment by trained analysts and designated as visible, or not visible, at the RAL.

