July 2004
Cleaning After a Media Fill

For any equipment for which cleaning validation is complete, any intervention in the standard manufacturing process should require a consideration of the effect of that intervention on the cleaning validation for that equipment. This applies to dealing with cleaning and releasing equipment following a *media fill* for an aseptic processing line. Following the media fill, there are several questions (relating to cleaning validation) that should be asked:

1. How shall we clean the equipment?
2. What are the acceptance criteria for release of the cleaned equipment?

Same cleaning process

To determine how to clean the equipment, the first choice for cleaning would be to use the *already validated cleaning process*. This can be done by lab studies, for example, to demonstrate the same conditions of time, temperature, cleaning agent and cleaning agent concentration (that is, the same conditions as in the validated cleaning method) are effective in cleaning the media from surfaces.

If use of the *same* cleaning process can be established, then there are at least two options for setting *acceptance criteria* for cleaning following the media fill. If measurement of TOC were used as one of the acceptance criteria in the product cleaning validation protocol, then one option is to establish that same TOC criteria for the media fill. The logic here is that if a TOC value were acceptable for cleaning of a drug product, then that same TOC value would also be valid for a non-drug product (the media). A second option may be applicable if TOC were not an analytical tool for the product cleaning validation. This option would be to establish some arbitrary TOC value, such as 10 ppm carryover of media to the next product or 10 ppm of media in any analytical sample. In both these cases, the equipment would be tested following cleaning by evaluating TOC (as well as other relevant criteria, such as cleaning agent, bioburden, endotoxin, and visually clean).

Note that in the former case where the TOC limit is established based on the drug product TOC, it may be possible to "group" the media with the manufactured drug product(s). If one can establish that the media is easier to clean than the previously validated drug product(s), then it becomes possible to claim that the previous cleaning validation of the drug product(s) applies to cleaning following a media fill. If one considers using such a grouping strategy, then grouping conditions, and specifically conditions for addition of a new product to an established group, should be described in appropriate documents (policies/procedures).

New cleaning process

If a *new cleaning process* were to be used, a strong preference should be made to use the existing (validated) cleaning process but with *more aggressive cleaning parameters*. For example, it may be the same cleaning process for a longer time, or it may be the same cleaning process at a higher detergent concentration. This is highly preferred because it simplifies the validation or verification process. The acceptance criteria for the media could be established as discussed before, using TOC as a measurement. If the same cleaning agent were used, then the acceptance criteria for the cleaning agent could be exactly the same as in the validated cleaning process (the fact it is used at a higher concentration or for a longer period of time does not affect setting its

limit). Note that if the cleaning process is the same but with more aggressive conditions, then it is *not* possible to group cleaning of the media with cleaning of drug product.

If the new cleaning process involves a *new cleaning agent*, then limits will have to be established for the new cleaning agent. An analytical method will have to be established and validated. In addition, recovery studies should be performed using the new analytical method and the new cleaning agent. It should be clear that this option of using a new cleaning agent should generally be avoided. The only situation where a changed cleaning agent might be feasible is where the validated process uses an aqueous cleaning agent and where the media can be cleaned with water alone. Note that with this case also, any grouping strategy with the validated cleaning process is *not* allowed.

Documentation of Effectiveness

Note that in either case (using the same cleaning process or a new/modified cleaning process) one will need to decide how to handle the documentation of effectiveness of cleaning following the media fill. As mentioned earlier, one strategy is to actually group the cleaning with a previously validated cleaning process for drug products. This is only possible if the identical cleaning process is used for the media and if the media is not the most-difficult-to-clean product. If such grouping is not possible or practical, then establishment of effectiveness of cleaning following the media fill can be done in either a verification mode or in a validation mode. If a media fill is performed on a quarterly basis, a validation protocol can be written to cover three (or whatever number is required to establish consistency) cleaning processes.

The purpose of this Cleaning Memo is to not to specify what should be done for cleaning for a media fill. Rather the purpose is to clarify issues that might arise in selecting a cleaning process and documenting effectiveness for media fills. In addition to the options presented, there may be other strategies to achieve the same goal.