

## January 2015 Regulatory Status of “Visually Clean Alone”

Recently there has been a lot of discussion on an internet forum about the acceptability of “visually clean alone” as an acceptance criterion. I believe this is based on the recent proposed changes to the EU’s GMP Annex 15 on “Qualification and Validation”. Section 9.2 of that proposed document reads in part:

“A visual check for cleanliness may form an important part of the acceptance criteria for cleaning validation; however, it is not acceptable for this criterion alone to be used.”

I believe this Annex 15 statement might be based on a similar statement in an FDA Human Drug CGMP Note of June 1998 that states:

When determining the acceptance limit, relevant factors generally include: (1) Evaluation of the therapeutic dose carryover; (2) toxicity of the potential contaminant; (3) concentration of the contaminant in the rinses; (4) limit of detection of the analytical test method; and, (5) visual examination. While we suggest that these factors be considered, relying only on visual examination would not be scientifically sound.

It is the word “only” in the FDA statement and “alone” in the EU statement in draft Annex 15 that I will focus on.

In discussing this issue, we should also consider the PIC/S recommendations (PIC/S PI 006-3) that states the following:

Carry-over of product residues should meet defined criteria, for example the most stringent of the following three criteria:

- (a) No more than 0.1% of the normal therapeutic dose of any product will appear in the maximum daily dose of the following product,
- (b) No more than 10 ppm of any product will appear in another product,
- (c) No quantity of residue should be visible on the equipment after cleaning procedures are performed. Spiking studies should determine the concentration at which most active ingredients are visible,

Just for clarification, the PIC/S document does list a fourth criterion; however, that fourth criterion is a special case that applies only to certain highly toxic actives. I think it is clear that the “most stringent” criterion only includes the first three criteria (that are given above).

Now the most interesting thing about this PIC/S statement is that it seems to allow for the possibility that visually clean could be the most stringent criterion, and could be used without the other two criteria (0.1% dose and 10 ppm). However, and I think the critical thing is that it cannot be used in this way “alone”. That is, in order to use it as the most stringent criteria one must do something not regularly done, and that is to perform spiking studies to determine the visual limit. Furthermore, although it is not stated in the PIC/S recommendations, in order for visual examination to be the most stringent, the visual limit must be at or below

the equivalent limit in  $\mu\text{g}/\text{cm}^2$  determined by both of the other two criteria. A third condition for using visually clean alone is that critical surfaces must be available for visual examination.

Therefore, my interpretation is that if one is using visually clean as the sole acceptance criterion, it is not being used “alone” if it is supplemented by a spiking study to determine the visual limit. Some may not agree with my analysis; however, I believe it is logically and scientifically sound.

I realize this may be reading more into the FDA statement and the EU Annex 15 statement than intended. However, it has been something I have written about in more detail in the past. In my August 2010 Cleaning Memo, I discussed (in a different context) possible interpretations of the PIC/S statement, including whether spiking studies were required if visual examination were used to supplement swab and/or rinse sampling with limits calculated by the more stringent of the 0.1% dose and 10 ppm criteria. Please refer to that document for further discussion of these issues.

Also, note that this discussion is an update of a similar discussion of the topic on rinse sampling alone in my November 2004 Cleaning Memo. I think this suggests that there is nothing new under the sun for cleaning validation (except perhaps for *health*-based limits).