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## Re: Cleaning Validation - Rinse Sample Limit

- *To:* "PharmSciTech" <[PharmTech@www2.pharmweb.net](mailto:PharmTech@www2.pharmweb.net)>
- *Subject:* Re: Cleaning Validation - Rinse Sample Limit
- *From:* [ed\\_white@baxter.com](mailto:ed_white@baxter.com)
- *Date:* Wed, 3 May 2006 00:05:01 +0100
- *Delivery-date:* Wed, 03 May 2006 00:04:54 +0100
- *Envelope-to:* [hm0068@www.pharmweb.net](mailto:hm0068@www.pharmweb.net)
- *Operating-System:* PharmWeb - <http://www.pharmweb.net>
- *Reply-To:* "PharmSciTech" <[PharmTech@www2.pharmweb.net](mailto:PharmTech@www2.pharmweb.net)>
- *Sender:* <[PharmTech@www2.pharmweb.net](mailto:PharmTech@www2.pharmweb.net)>
- *Sponsors:* PDA

Finbar:

I think you are on the right track in considering ICH Q3A, "Impurities in New Drug Substances."

If you know what impurities would be expected to carry over from batch to batch, taking degradation due to the cleaning process into account, you can put together a formal risk assessment for the product carryover, based on the effect of the impurities on the process, on the product, and on the patient. A maximum value for carryover would probably be the ICH Q3A limit for identification of impurities (0.10%).

Based on the 0.10% identification threshold for organic impurities, I would base my Maximum Allowable Carryover (MACO) calculation on NMT 0.10% carry-over from batch-to-batch, using TOC or another suitable assay for measurement. I would use the bioreactor protein production in grams as the starting point. This is assuming a bioreactor or fermenter process, where further downstream purification is expected to occur. As stated by Dr. Kirsch, the actual MACO calculations can be found in PDA TR29, or in Destin LeBlanc's book.

As an example, if you produced 100 grams of protein in a bioreactor batch, your MACO into the next batch would be 0.1 gram of protein.

You would assume this 0.1 gram of protein would be distributed evenly across the bioreactor surface. If you were to rinse the bioreactor with 10 liter of WFI, assuming 100% recovery, your Maximum Allowable Carryover would be 0.01 gram / liter, or 10 microgram / mL.

Obviously, you would have to factor in the actual rinse water recovery, assay recovery, etc., to come up with your final limits.

Obviously, if your expected residues or degradants are expected to be detrimental to the patient or process, you would take a look at toxicity data such as the LD50 or NOEL limits, which could result in limits tighter than the ICH Q3A Impurities limits.

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Find purpose; the means will follow. -Gandhi

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