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cleaning validation criteria

- *To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Subject*: cleaning validation criteria
- *From*: "Hiroaki Matsumoto" <matsumoto.hm@om.asahi-kasei.co.jp> (by way ofPDA Sci-Tech Forum <moderator@pda.org>)
- *Date*: Mon, 22 Jul 2002 08:40:46 -0400
- *Delivery-date*: Mon, 22 Jul 2002 13:32:49 +0100
- *Envelope-to*: hm0068@www.pharmweb.net
- *Operating-System*: PharmWeb - http://www.pharmweb.net
- *Reply-To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Sender*: <PharmTech@www2.pharmweb.net>

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Dear forum,

Could anyone please advise regarding a maximum permitted criteria after
cleaning
of multi-purpose facility. Recently a maximum 10ppm criteria has been
familiar,
as indicated in several reports in case an allowable level of
cross-contaminant(s)
in a next-product is considered. A criteria, however should be established
according
to toxicity or pharmacological properties. How do you think about a
relation between
these threshold and maximum permitted criteria in cleaning validation? For
example,
is a cross-contaminant level of lower 1/10000 of its pharmacological or
toxicological
threshold in next-product permitted? I hope to know an allowable
cross-contaminant level
associated with its pharmacological or toxicological properties.

Any comments would be greatly appreciated.

H.Matsumoto
matsumoto.hm@om.asahi-kasei.co.jp
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RE: cleaning validation criteria

- *To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Subject*: RE: cleaning validation criteria
- *From*: "Cleaning Validation Technologies" <destin@cleaningvalidation.com>(by way of PDA Sci-Tech Forum <moderator@pda.org>)
- *Date*: Tue, 23 Jul 2002 09:23:26 -0400
- *Delivery-date*: Tue, 23 Jul 2002 14:16:51 +0100
- *Envelope-to*: hm0068@www.pharmweb.net
- *Operating-System*: PharmWeb - http://www.pharmweb.net
- *Reply-To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Sender*: <PharmTech@www2.pharmweb.net>

H. Matsumoto:

The traditional approach to setting limits for drug actives in multi-use equipment has been based on dose-based (pharmacological) calculations. For items such as cleaning agents, the limits are usually set based on toxicological properties. Your reference to the "10 ppm criteria" needs careful application. As presented by Fourmen and Mullen in their 1993 Pharm Tech paper, this 10 ppm is NOT 10 ppm in the analytical sample, but rather 10 ppm in the subsequently manufactured product. Furthermore, this 10 ppm could only be a "default" limit if it were lower than the dose-based (or toxicity-based) calculation.

Regards,

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destin@cleaningvalidation.com
www.cleaningvalidation.com
phone: 210-481-7865
fax: 210-481-7496

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RE: cleaning validation criteria

- *To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Subject*: RE: cleaning validation criteria
- *From*: "Walsh, Andrew W {Vali~Nutley}" <ANDREW_W.WALSH@ROCHE.COM> (by wayof PDA Sci-Tech Forum <moderator@pda.org>)
- *Date*: Fri, 26 Jul 2002 10:24:20 -0400
- *Delivery-date*: Fri, 26 Jul 2002 15:17:06 +0100
- *Envelope-to*: hm0068@www.pharmweb.net
- *Operating-System*: PharmWeb - http://www.pharmweb.net
- *Reply-To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Sender*: <PharmTech@www2.pharmweb.net>

Hi Hiroaki,

The use of the "10 ppm" and "1/1,000th dose" as cleaning validation limits seem to have become "industry standards". They come from an article published by Eli Lilly in 1993. But they do not have any universal application. Even though many companies use them, I would not turn to them.

Ultimately it is really up to you (your company)to decide what an appropriate limit is for any of your products in other products. Your own company should know more than anyone about your products. My personal view is that you need to have your own Medical and Toxicology departments set limits for each product based on their knowledge and understanding of the products. Each product should have a risk analysis done and limits set from them. In fact, this risk analysis should decide whether a product should be manufactured on dedicated equipment or is safe on multi-use equipment. In my opinion, all such decisions (limits, dedication etc.) should be made based on medical and scientific knowledge of the specific products. Don't guess at it with arbitrary limits such as "10 ppm" and "1/1,000th dose".

When you have obtained limits from your Medical/Toxicolgy departments, you can perform cleaning validations with much greater confidence that your limits are truly "safe" ones. Clean your equipment well, record how you performed the cleaning, and analyze your samples. Typically your analytical results will be much lower than these limits. After you have collected your analytical data, you can then statistically analyze them and set a statistically based limit for all future cleanings.

In my mind, you should clean to the best of your ability (without killing yourself) and all equipment should be cleaned to this level. If a risk analysis for a new product shows that you will need to clean lower than you know you can statistically achieve in practice, then you need to dedicate that product.

Regulatory agencies (at least the FDA) are starting to question the limit concepts currently used by many companies in cleaning validation.

Andrew Walsh
Andrew_W.Walsh@roche.com

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RE: cleaning validation criteria

- *To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Subject*: RE: cleaning validation criteria
- *From*: "Cleaning Validation Technologies" <destin@cleaningvalidation.com>(by way of PDA Sci-Tech Forum <moderator@pda.org>)
- *Date*: Mon, 29 Jul 2002 10:53:49 -0400
- *Delivery-date*: Tue, 30 Jul 2002 09:03:05 +0100
- *Envelope-to*: hm0068@www.pharmweb.net
- *Operating-System*: PharmWeb - http://www.pharmweb.net
- *Reply-To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Sender*: <PharmTech@www2.pharmweb.net>

Andy:

In an ideal world, part of your advice for setting limits (starting from scratch and having the medical and toxicology groups of companies set limits based on their knowledge) may work. However, if we are to get any cleaning validation work done, people most likely will have to start with the traditional Fourmen and Mullen approach, and then if they have any information to set more stringent limits, they should do so.

The issue of the FDA being concerned with how people set limits is, to the best of my understanding, based on the fact that some companies do not consider non-dose related information, such as allergenic properties, cytotoxic properties, or reproductive hazard concerns, in setting limits. These are some of the "additional information" things that should be considered in setting limits.

Ultimately, each company is going to set limits based on their own risk analysis. However, while the 1/1000 dose criteria may have been somewhat arbitrary in the beginning, it has been a well accepted consensus starting point for setting limits. Throwing it out at this time is probably not a wise choice for the industry or for regulators.

Regards,

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RE: cleaning validation criteria

- *To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Subject*: RE: cleaning validation criteria
- *From*: "Walsh, Andrew W {Vali~Nutley}" <ANDREW_W.WALSH@ROCHE.COM> (by wayof PDA Sci-Tech Forum <moderator@pda.org>)
- *Date*: Thu, 01 Aug 2002 09:28:54 -0400
- *Delivery-date*: Thu, 01 Aug 2002 14:22:55 +0100
- *Envelope-to*: hm0068@www.pharmweb.net
- *Operating-System*: PharmWeb - http://www.pharmweb.net
- *Reply-To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Sender*: <PharmTech@www2.pharmweb.net>

Hi Destin,

I do understand when you say companies need a place to start. However, my experience has been that once a path has been selected, most people are very reluctant to change it. So I think it's better to start with the best choices right from the beginning. What got the industry started in cleaning validation 10+ years ago may no longer be currentGMP. So it's probably a wise choice to think through how we set limits and not default to arbitrary ones.

Personally, I wouldn't consider allergenic properties, cytotoxic properties, or reproductive hazard concerns to be "additional information" but rather the "drivers" as to setting limits and for the decision to dedicate products. The regulatory agencies have always expected us to know our products and our processes. We're supposed to be the experts. We should tell them what a "safe" limit is and when we need to/don't need to dedicate equipment/products and why. Not that we use 1/1,000th so everything is OK. How are they supposed to know that's safe if we don't know??

FDA is not only questioning these limits for the reasons you mention, but have issued 483s for using 10ppm for not being scientifically based (see GMP Trends) and Ann deMarco of the Philadelphia office presented a paper at CASA last year challenging the whole concept of the MAC (maximum allowable carryover) calculations as contrary to GMPs. So as I see it today, if you simply pick 1/1,000th and/or 10ppm you will eventually be challenged to defend why it is appropriate. So I think it's better to start off with setting your limits based on medical and toxicological information that is scientifically defendable. Every product that makes it to market has toxicological and safety information in place already. I think it would be very hard to tell an inspector that it's fine to manufacture a teratogen in the same equipment used to manufacture pre-natal vitamins because the swab samples met the 1/1,000th dose limit. I think they would want more assurance than that. And where do you draw the line as to where it's OK to use 1/1,000th and where it's not? So eventually I see that ALL limits will need to be established backed by medical and toxicological data.

And I just can't subscribe to the notion that we should keep the 1/1,000th limit because it is widely used in the industry today. As I heard Jim Agalloco once say at a conference - "Even if a 1,000 people do a foolish thing....it's still a foolish thing".

Sorry I missed you at the 9th annual IIR conference.

Best regards,

Andy Walsh
Andrew_W.Walsh@roche.com

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RE: cleaning validation criteria

- *To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Subject*: RE: cleaning validation criteria
- *From*: "Destin LeBlanc \(E-mail\)" <destin@cleaningvalidation.com> (by wayof PDA Sci-Tech Forum <moderator@pda.org>)
- *Date*: Fri, 02 Aug 2002 09:03:11 -0400
- *Delivery-date*: Fri, 02 Aug 2002 13:59:03 +0100
- *Envelope-to*: hm0068@www.pharmweb.net
- *Operating-System*: PharmWeb - http://www.pharmweb.net
- *Reply-To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Sender*: <PharmTech@www2.pharmweb.net>

Andy:

It is necessary to put the regulatory challenges in perspective. The challenge to "10 ppm" is a valid challenge if the 10 ppm "default" is being misused (as is commonly done). The 10 ppm "default" limit as proposed by the Fourman and Mullen was not an "either/or" situation. Their formulation was to calculate the dose-based limit, and if 10 ppm was less than the dose-based limit, then you would default to the lower value. Many people see this as an either/or situation, and pick the 10 ppm without a comparison to the dose-based limit.

In terms of the deMarco challenge to the MAC concept, that challenge may be appropriate, but the presentation of the challenge (in the version of the paper I saw) was flawed in that the calculation was done incorrectly. The MAC calculation is based on 0.001 of the minimum dose of the active of the product you are cleaning in the maximum dose of the next drug PRODUCT. The MAC calculation given in that paper is calculated based on the maximum dose of the next drug ACTIVE. For the specific example used, this mistake results in the the MAC being increased by a factor of greater than three logs. It's unclear whether the incorrect use of the MAC calculation came from a specific company being investigated or not, but in any case the calculation, as it is supposed to be used, was not used.

I'm sorry you interpreted my "additional" information as "optional" information. That was not my intention. The intention was that "additional" just means information in addition to the dose-based calculation. It is still prudent to do a dose-based calculation, and then determine whether there are any other issues or information that would cause that level to be a concern, and therefore to be lower.

I don't believe there is anything "foolish" about establishment of limits in this way. What we should question is companies (people?) misusing these concepts.

If nothing else, this exchange will hopefully increase the awareness within the industry of this issue.

Regards,

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Re: cleaning validation criteria

- *To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Subject*: Re: cleaning validation criteria
- *From*: "Walsh, Andrew W {Vali~Nutley}" <ANDREW_W.WALSH@ROCHE.COM> (by wayof PDA Sci-Tech Forum <moderator@pda.org>)
- *Date*: Mon, 05 Aug 2002 09:26:35 -0400
- *Delivery-date*: Mon, 05 Aug 2002 14:18:53 +0100
- *Envelope-to*: hm0068@www.pharmweb.net
- *Operating-System*: PharmWeb - http://www.pharmweb.net
- *Reply-To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Sender*: <PharmTech@www2.pharmweb.net>

Destin,

I was not saying using these limits and calculations are foolish (I would still use some of them), I was saying using them because everyone else does is not a good argument.

And although I say I would still use some of them, I would not use them the way they are used today.

Ann deMarco is still correct in her demonstration regardless of employing an active, rather than a product, in her calculations. It's a minor point. It's not always going to be off by 1,000 as you say. It depends on the maximum daily dosage of product B which is not always 1,000 higher than the active amount. A low potency drug in a tablet can be almost all active and I doubt the maximum daily dose is 1,000 tablets. Regardless, she was showing how wide the MAC can vary across low to high potency drugs and her argument still holds. The MAC can be anything and even absurdly high as she showed. I have seen this type of thing even when calculating using maximum daily doses.

The problem as she puts it is that some "Firms have drastically reduced equipment cleaning efforts based on the MAC concept" and "It is this interpretation by various companies that prompted a review of these formulas by the authors". I think everyone of us knows there are people out there who will tell you "If the limit is 100 and I got 99.99 - I pass!!" It is this mentality that concerns Ann deMarco (and myself too). Unfortunately, there's a few companies out there who would use the MAC to validate slovenliness.

The use of 10 ppm is flawed however you use it. Why is it not 5 ppm or 1 ppm?? There's no good answer to that. And the problem doesn't go away when you combine 10 ppm with the 1/1,000th calculation. All that happens then is that the 10 ppm criteria results in stricter limits for your low potency drugs. If I calculated a limit in a batch for a high potency drug and it comes out to 9 ppm I do nothing. But if I calculate a limit for a low potency drug and it comes out high I drop it to 10 ppm. Basically the same limit as my high potency drug. So I'm more strict with low potency drugs, which have less pharmacological concerns, than with my high potency drugs

which do. That's backwards. Where this really starts to become glaring is when you analyze your data and start writing your CV report. I have always calculated the log difference between my data and the limit to see how far away my data is and assess my actual margin of safety. But when using 10ppm you cannot assess how much you reduced the residues of a low potency drug from its true safe level.

I started in cleaning validation in 1994 and quickly adopted the 1/1,000th & 10ppm mantra. But after a few years I started to doubt the wisdom of that choice. The 10 ppm limit was the first thing I noticed being off base. Then I noticed that adding "safety factors" to your limits did nothing to reduce residues or improve safety. The funny thing is everyone talked about how to tighten limits by adding "safety factors" but no one talked about how to clean better. In my mind, if you want to increase safety, don't add safety factors to your limits - clean better.

Today I think Cleaning Validation should be approached differently. I recommend the following:

1 - Develop analytical methods with LOQs/LODs as low as possible.
2 - Do cleaning assessment runs on your hard to clean products with the LOD as a target.
3 - Optimize your cleaning procedure and collect your data.
4 - Set a statistically based process limit based on the assessment data.
5 - Perform your cleaning validation.
6 - Compare your data to a medically/toxicologically derived limit and calculate the log difference between them. That value is your true margin of safety.

I also would like to see more companies start using TOC to assess cleaning procedures. It's a great way to show what amount of total residue is present across the board. It also allows you to compare cleanings between products, between equipment, between areas, between sites and even between companies.

I hope this was helpful, and I agree the industry should start discussing it more.

Andy
Andrew Walsh
andrew_w.walsh@roche.com

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RE: cleaning validation criteria

- *To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Subject*: RE: cleaning validation criteria
- *From*: "Destin A. LeBlanc" <destin@cleaningvalidation.com> (by way of PDASci-Tech Forum <moderator@pda.org>)
- *Date*: Thu, 08 Aug 2002 09:08:17 -0400
- *Delivery-date*: Thu, 08 Aug 2002 14:01:29 +0100
- *Envelope-to*: hm0068@www.pharmweb.net
- *Operating-System*: PharmWeb - http://www.pharmweb.net
- *Reply-To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Sender*: <PharmTech@www2.pharmweb.net>

Andy:

If there are firms that are being slovenly in their cleaning, the response is not to tighten the standards, but rather hold their feet to the fire on the existing standards.

I have seen no information that suggests that current "standards" for setting limits are inadequate. Those standards may change over time, but that is part of the "current" in cGMP. What I have seen is firms misapplying those standards. And, education and training is part of that correction.

Perhaps where you and I disagree is that I believe if you set limits, and they are set with adequate justification, and you meet those limits, that is adequate for compliance purposes. I don't think anybody sets limits at 100 units, and does validation expecting to get 99.99. My experience has been that most people design their cleaning process so that residues are well below their acceptance limits. Clearly your cleaning process should be designed to pass any acceptance limit with a wide margin. But if it passes with a narrow margin, it still passes, but it probably means that you are going to have to do more monitoring (or process improvements under change control).

Yes, 10 ppm is arbitrary. But so is then limit for identification of impurities in drug actives. And so is the SAL for sterility validation. One can always ask why not a however value. At least in cleaning validation, the 10 ppm value is only used if it is below the dose-based limit (or at least it should be used that way). I don't understand the rationale behind your objection.

In regards to the issue of different margins of safety for low and how potency drugs, isn't the issue whether you are at a safe level, not how far below the safe level you are. Yes, you want to be well below the limit to help assurance of passing the validation, but the fact that one is lower than the safe limit by a factor of 100 and the other is below its safe limit by a factor of 10 should not be indicative of inadequate limits setting or inadequate cleaning. Also, it is important to distinguish between two uses of "margin of safety": one is the margin of safety between the residue measured and your established limits, and the other is the margin of safety

between the established limit and any scientifically determined safe level. The latter is confused by the fact that the "safety factor" used in MAC calculations actually is a combination of a "safety factor" and a "conversion factor" (that use, it partly applies a conversion factor to a dose to bring it to a safe level, and partly is applying a safety factor on top of that).

In terms of whether the deMarco objection is correct or not, I believe if you want to object to a formulation like the MAC, it should be applied accurately. The deMarco example had a MAC of 300,000 grams into a next batch of 250,000 grams. That certainly is dramatic. But if applied correctly, the MAC would result in an amount less than 300 grams in the next batch. That may be unacceptable, but is a far cry from 300,000 grams. Even if in some case it results in large carryovers, the "defaults" of "10 ppm in the next product" and "visually clean" equipment will make for more stringent cleaning. In the example given in the deMarco paper, the MAC based on a 10 ppm default would have been 2.5 grams. It seems that if the calculation and the defaults are correctly used, the impact of the argument is not as great.

Where deMarco is on target is in taking into account other effects (other than doses), such as allergenic effects and reproductive hazard concerns. Raising those issues is a significant contribution to the discussion.

The approach you specify can be used for certain products. However, for new products, how do you develop enough data to set a "statistically based process limit"?

I would encourage companies to improve all their processes to enhance the quality and safety of their products. However, it is necessary to evaluate the impact different improvements may have on improved safety and quality, and begin the process there. If changing the way we set residue limits comes out near the top of then list, then let's do that. However, for cleaning purposes, I suspect the bigger impact on safety, quality, and compliance will come from adhering strictly to the existing methods.

In the interest of not extending this on this forum (I think we both have made our best arguments), if you respond to this on the PharmWeb, I promise not to make another response in reply. However, I may reply off-line to you.

Regards,

Destin

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destin@cleaningvalidation.com
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(210) 481-7865

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RE: cleaning validation criteria

- *To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Subject*: RE: cleaning validation criteria
- *From*: "Walsh, Andrew W {Vali~Nutley}" <ANDREW_W.WALSH@ROCHE.COM> (by wayof PDA Sci-Tech Forum <moderator@pda.org>)
- *Date*: Mon, 26 Aug 2002 09:19:54 -0400
- *Delivery-date*: Tue, 27 Aug 2002 10:27:09 +0100
- *Envelope-to*: hm0068@www.pharmweb.net
- *Operating-System*: PharmWeb - http://www.pharmweb.net
- *Reply-To*: "PharmSciTech" <PharmTech@www2.pharmweb.net>
- *Sender*: <PharmTech@www2.pharmweb.net>

```
Destin,

I will reply since some things need clarification.

I can't agree with your position that since there are other current
standards that are indefensible that adding some more is OK. I also don't
think we should steadfastly hold onto the status quo long when the quo has
lost its status.

You write: "The approach you specify can be used for certain products.
However, for new
products, how do you develop enough data to set a "statistically based
process limit"?"

Actually this is one of the best uses for a statistically based limit. In
my opinion all equipment should be cleaned to the same level of
cleanliness. After you have completed CVs on your "worst case" products you
should establish a database, statistically analyze your data and set
limits. All products, "new" or other existing ones, must meet this limit.
Make the "new" product, clean the equipment, and determine if residues are
equal to/less than this limit. Then do an assessment of how "safe" the data
is. (Of course, you should have already determined whether the product
should be allowed on the equipment in the first place....).

Best regards,

Andy
Andrew_W.Walsh@roche.com
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Destin LeBlanc

From: Destin A. LeBlanc <destin@cleaningvalidation.com>
Sent: Wednesday, September 04, 2002 12:39 PM
To: Andrew_W.Walsh@roche.com
Subject: Cleaning validation criteria

Sensitivity: Confidential

Andy:

First let say that this is not going to PharmWeb. As I said in my last posting, I think we have both put forward our best arguments. However, I reserved the right to reply to you personally, so I am doing so now.

My position is NOT "since there are other current standards that are indefensible that adding some more is OK". That's your interpretation (or your spin) of my position. My position is that "many standards have an element of arbitrariness to them, and that doesn't make them unacceptable or unwise."

I guess rather than attributing extreme positions to me (the current standards are in fact defensible), you could take a more charitable position as you attack what you perceive as a misuse of limits calculations (and whatever the standards are, there will be people who will misuse them).

I don't really think we are too far off. Here is my summary of your position, based on several of your postings. Let me know if I am in error on the basic position.

"Clean the best you can, hopefully down to the LOD of the best available technique; do a statistical analysis, and set your limits based on that.
After you do that, have the regulatory/toxicology group evaluate that limit to see if it is reasonable".

I have no problem with that approach. However, I believe that as part of the evaluation by the regualtory/toxicology group, they will use the 1/1000 dose-based calculations among other considerations. However, here is a summary of another approach:

"Set your limits based on what the regualtory/toxicology group evaluates to be reasonable. As part of the evaluation by the regulatory/toxicology group, they will use the 1/1000 dose-based calculations among other considerations.
Then design a cleaning process to clean below that limit."

I suspect that in 99% of the cases, the results in a cleaning validation protocol will be the same in terms of measured residues independent of what approach is taken.

Andy, I also perceived that you object to the 1/1000 factor being called a "safety" factor. You have written several times that the true safety factor is how much you are below your acceptance limit. I agree with you; the 1/1000 "safety" factor is really a "conversion" factor to take a dose down to a safe level. However, as a practical matter, I don't think the pharmaceutical industry is going to change the terminology and call it a conversion factor rather than a safety factor. I think it is worth pointing out that the safety factor is really a conversion factor (as I do in my seminars). I think it is also reasonable to try to design a system to clean significantly below the acceptance limit.

After all this, Andy, it appears to me that we are saying similar things.
Why then do you promote my position as "indefensible" and promoting a "status quo that has lost its status." Anything you can do to help me understand would be beneficial.

Regards,

Destin

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-----Original Message-----
From: PharmTech@www2.pharmweb.net [mailto:PharmTech@www2.pharmweb.net]On Behalf Of Walsh, Andrew W {Vali~Nutley} (by way of PDA Sci-Tech Forum <moderator@pda.org>)
Sent: Monday, August 26, 2002 8:20 AM
To: PharmSciTech
Subject: RE: cleaning validation criteria

Destin,

I will reply since some things need clarification.

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Make the "new" product, clean the equipment, and determine if residues are equal to/less than this limit. Then do an assessment of how "safe" the data is. (Of course, you should have already determined whether the product should be allowed on the equipment in the first place....).

Best regards,

Andy
Andrew_W.Walsh@roche.com