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Public Comments to the Ocular Expert Panel convened by ICCVAM at the meeting:

"Expert Panel Evaluation of the Current Validation Status of *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants"

January 12, public comment session #1:

1) Yesterday, there was discussion around the use of the word "accuracy" [and whether it should be used with respect to concordance with the Draize rabbit data]. It might seem like a semantic point but it isn't. It bothers people because the use of "accuracy" seems to denote a desire to cling to the animal test as the gold standard. Last night, I consulted several dictionaries and the most common definition I could find for accuracy was "the quality of nearness to the truth or the true value." So, regardless of the definition of accuracy given in an ICCVAM glossary, to most people, use of the word "accuracy" to describe agreement with the rabbit test implies that the rabbit test represents the "truth."

   I agree with those who want to reserve the word accuracy for nearness to the true value, which is the human response, but if that's not done, for clarity, it's crucial to qualify the word accuracy every time with either "accuracy with respect to the Draize eye test" or "accuracy with respect to human data."

   We've come a long way from assuming that animal data is the gold standard and our language needs to reflect that.

2) The rest of my comments pertain to the BRDs (background review documents) and the process here.

   It seems that there has been confusion regarding the scope and content of the BRDs. I agree with Sara (Amundson of the Doris Day Animal League) and others that the documents far overstepped their bounds and led the process.

   To my mind, the BRDs should have presented data to the expert panel and asked them to consider it with three outcomes in mind, concluding that:

   1) the method was generally scientifically valid
   2) the method was scientifically valid in certain circumstances or with limitations
   3) the method was scientifically invalid or not ready to be useful in any circumstance

Any consideration of improvements or optimizations is secondary to giving an opinion on the current validity of a method.

But instead, the BRDs not only presented the data but drew their own conclusions and recommended additional optimization and validation studies for every method.

And so the panel has had a lot of focus on possible improvements to or tweaks of these methods but has not drawn clear conclusions on the current validity and has left some of methods in limbo, which is a step backwards for these methods, and is really a disservice to them.

These methods have been in use for around 20 years and have been accepted by some European countries for around a decade, and so, are currently accepted in the E.U. through mutual acceptance of data. Some have been through laboratory validation studies. They've stood the test of time, which is the only test of accuracy we've applied to the Draize test. And the numbers we've seen on them –despite the fact that certain data are missing and other problems– are nonetheless all pretty good.

The big picture is that these are long-standing and in some cases, very widely used methods, bases in 3 cases on **actual animal eyes**, that are **only** being considered as **positive screens** for just **severe irritants** and corrosives. This should be a slam dunk.

If this process can't validate at least one of these methods as a partial replacement now, in 2005, and instead says each one needs years of further studies, it would seem that there's very little hope of ever getting to the harder stuff –mild irritants– and that a complement replacement of the Draize test probably won't happen in our grandchildren's lifetimes.

And as Sara (Amundson of the Doris Day Animal League) mentioned, if this process takes these tests backwards, not only will ICCVAM not receive new nominations, people will purposely try to lay low and hope that ICCVAM doesn't notice their methods.

I would like to wrap up by asking this expert panel to please approach these tests by asking yourself:

> *Is this test scientifically valid and potentially useful as a positive screen for corrosives in any definable set of circumstances and if so, can we retrospectively validate it today on the basis of the data we've seen, combined with our scientific judgment?*

We could always wish for more data but scientific judgment can compensate for gaps in data and that's what I believed this panel was convened here to do.

Even if you can think of ways to better characterize and optimize the method, which we could do for any test including the Draize eye test as the IRE panel recommendation just pointed out, can we send a clear message **today** that the method is basically valid?

If you truly don't think that the method has any scientific merit even with limitations imposed upon it, then of course you must conclude that, but please be aware as you make that important decision of the impact on the ICCVAM process if not a single one of these tests is validated here.

Thanks so much for your time.

January 12, public comment session #2:

I was pleased with the presentation of the BCOP group's panel recommendations – it seemed to me a reasonable approach that lead to what I saw as a positive conclusion. What I heard from Dr. Stitzel's presentation is that the BCOP is "acceptable for use" with certain caveats, but that those caveats can be resolved retrospectively with existing data and do not require additional validation studies because the BCOP is "already validated." I think this is about as good as it gets.

I would just like to ask if the panel –instead of saying "acceptable for use"– can specifically use the term "considered scientifically valid" or better yet "validated" for greater clarity than the term "acceptable for use" if validity is indeed what the panel means.

Thank you.

January 12, public comment session #3:

We just had a lot of discussion over "validation" and whether this panel was allowed to conclude that the method was valid. We heard from the chairperson of this panel that "the question you're being asked, is this test valid, is not the question before the group." But on the other hand, the very title of this meeting is "Expert Panel Evaluation of **Current Validation Status** of *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants." To me, "Current Validation Status" *means*: "valid", "not valid", that type of thing. The panel was given conflicting instruction as to this point and the fact that the discussion went on so long is a reflection of the lack of adequate instruction to the panel and of clarity in this process that I alluded to in my earlier comment. It was not clear what the outcome of this panel deliberation was meant to be, what they could conclude, what the point of this panel was, and so on.

I for one was very sorry to see even just the term "met the validation criteria" removed from the document, several times. But the main issue now is that there

needs to be more consistency and clarity in this process. To someone who just comes in as an expert on a particular method, the issue of whether this panel can call something "valid" might not seem important, but to those of us who follow the ICCVAM process –and the SACATM members on this panel seemed to be some of the people more concerned about this issue– it is crucially important to know what the outcome of this meeting was supposed to be because it is a model for other meetings that will be convened in the future, and if it isn't resolved, this lengthy discussion will have to happen at all future expert panel meetings. I believe that this expert panel should have been allowed to make a summary recommendation for each method to ICCVAM about their opinion on the validation status of the method and how it should go forward. But again, it's consistency and clarity in this process that's key. That's the last I'll say on this topic.

While I'm up here, I wanted to mention a few other things. This first is the process that went on around data collection and data exclusion. We heard from Bill Stokes that "When we put this data together in April, we felt that there were significant gaps in the data and we wanted your opinion on that." Why was this panel flown in from all across the world to opine on data with significant known gaps in it? Why wasn't a greater effort made to fill those gaps, especially with obvious sources such as the company in the UK that does IRE tests that was mentioned earlier? It also seemed like across the board, the approach to data inclusion was unnecessarily stringent and overly conservative and a **lot** of data was left out. The end result was that the conclusion of many of the BRDs was that additional time is needed to collect more existing data, and to conduct more studies, including new animal studies -- when instead there could have been a greater effort to include and use the data they already had.

The last point I wanted to raise was regarding the Draize test analysis that we got last Thursday or Friday. For the record, we have a lot of problems with that analysis, and the apparent bias in favor of the Draize tests throughout it in terms of assumptions that were made (such as assumptions about homogeneity of response, for example, within chemical classes). I also wanted to point out that the numbers presented, something like 14-15% variability, represent a low end at best because this analysis only included **intra-experiment** data –whereas, here, we're looking at variability in terms of **intra-laboratory** and **inter-laboratory** data– and also, it started from numerical timepoint scores–not from photographs I believe– and scoring of the Draize test is completely subjective and an important source of variability. So we believe the analysis represents a low end at best and we do not agree with it.

Thank you.