

Setting Early Development Specifications – Workshop Summary

It was generally agreed that setting early development specifications is an empirical process. There are no guidance's to follow although the ICH guidance's should be considered as an end point for the process. There is no clear rationale from a scientific perspective, due to lack of data, for what acceptance criteria should be. Participants used values that they "felt comfortable with" which were based on experience, judgment and precedent.

There was a wide range of practice across companies on what was considered appropriate for impurities/degradates in NCE's, from a low of not more than 2.0% total impurities to a high of not more than 5.0% total impurities with no individual impurity greater than 1.0%.

Most participants agreed that they, as a general rule, investigated and identified impurities when they occurred at much lower levels in spite of the filed acceptance criteria.

Although it was agreed that specifications should be chosen to ensure the safety and efficacy a large number of other factors influence the choice.

It was generally agreed that "lower" and/or "tighter" specifications were viewed as somehow indicating "quality" by both regulators and internal quality groups although there is no scientific basis for this view and that as key stakeholders in the process we needed to be more assertive in not succumbing to these pressures

It was generally agreed that refinement of specifications was appropriate as new data became available and as projects progressed into later stages of development. There was general agreement the process becomes a process of negotiations between the major stakeholders who included Safety Assessment, Regulatory Affairs, Internal Quality, Manufacturing, Analytical, Process Chemistry, Business/Management which was then followed by a final round of negotiations with the Regulatory Agencies

The group discussed some examples of how to manage the negotiations process

Last minute requests for tightening of acceptance criteria are sometimes received by companies very late in the review process and company management sometimes puts pressure on Specification Committees to accept the change request so as not to delay approval. Where appropriate company management should be made aware of the business consequences. In some cases tightening the acceptance criteria for a particular test may cause rejection of batches and the economic loss needs to be weighed against the economic impact of potential delays in approval.

When faced with a request by an agency to tighten a range or reduce a limit that is not considered defensible from a scientific point of view due to lack of data a successful strategy that has been employed by some companies is to request that the decision be delayed until enough data has been collected to statistically justify the requested change. This can be an agreed on number of batches or time period

Many participants agreed that their organization used the “what did they approve the last time” approach which tends to have an additive effect over time which was generally felt to be detrimental. A “zero based” specification setting approach was recommended.

It was generally hoped that the new Quality by Design initiatives that are currently under way will help bring a more scientific based approach to specification setting