

1 March 2012
EMA/CHMP/BWP/30584/2012
Human Medicines Development and Evaluation

Report on the expert workshop on setting specifications for biotech products

European Medicines Agency, London, 9 September 2011

Introduction

Setting specifications is an area of great interest to both the regulatory agencies and industry particularly as our knowledge of product and process continuously evolves. More experience in manufacture of recombinant proteins is being gained with the use of these types of products and the correlation of potential safety concerns with product variants and impurities. Analytical techniques are constantly being improved and products are becoming better characterised.

What to control is one of the key questions to consider for each product in establishing the specification. Information about the Critical Quality Attributes (CQAs) is defined during development. The criticality of controlling these in routine production should be assessed, but consideration should also be given to life cycle maintenance of specifications.

The **basis for setting acceptance criteria** for the release and in-process control (IPC) specifications must also be considered. How will it be possible to ensure that the variability in the production process is covered by the specification with the limited number of manufacturing scale lots that are available at the time of submission? Are these criteria reflected in the clinical experience with the product, or are the limits based on process performance alone?

The selection of the most suitable **statistical models** to define the acceptance criteria for different types of assays is another topic for discussion, but equally important is the understanding of the source of variability and the contribution not only from the process but also from the variability from the analytical methods.

With new and improved analytical technologies and techniques becoming available on an ongoing basis, the question of **how and where to control** process performance and product quality is also key. How is the link between methods and CQAs best established, are specific tests best performed as an IPC or as a component of final release testing. How can alert and action limits be utilised in controlling the process that would result in a suitable product quality?

The aim of the Workshop was to address some of the key topics on setting specifications from a regulatory and an industry perspective with the intention of fostering a discussion on these issues and, if possible, to arrive at a consensus view. For each session the topic was presented by a regulator and an industry speaker. The Workshop intended to bring together experts in the area. The sessions were interactive with the aim of drawing upon the experience of the participants during the discussions. It is hoped that the output from the Workshop will provide a useful reference source for future regulatory guidelines.

Notes from the workshop

Session 1 – What to control

Nanna Aaby Kruse (Danish Medicines Agency) provided the regulatory background on the issue. It is optional whether a company chooses to develop their manufacturing process by an enhanced approach, as introduced in ICH guidelines Q8, Q9 and Q10, or by a traditional approach. Nevertheless, the general concepts introduced by Quality by Design (QbD) to put emphasis on the design of the total control strategy for the product, is widely taken on board by the regulators, not only for the enhanced approach but also for the traditional product development.

The quality control system within a company is mandatory in accordance to Good Manufacturing Practices (GMP) (Directive 2003/94/EC, Article 11) whereas “what to control”, is described in requirements for a Marketing Authorisation Application (MAA), (Directive 2001/83/EC, Annex 1).

What to control is further outlined in the ICH Q6B guideline. It came into force in 1998 and is still considered to be a very valid guideline. The guideline outlines that a specification should be set for active substance and finished medicinal product (release and shelf-life). The specification is defined as *“a list of tests, references to analytical procedures and appropriate acceptance criteria. Specifications (...) should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.”* Furthermore, it outlines that the acceptance criteria set for the controls in the specification, among others, should be based on data from batches used in clinical trials. This is still considered fundamental in the establishment of a specification, enhanced development approach or not.

Specifications are only one part of a total control strategy designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterisation during development, adherence to GMP, a validated manufacturing process, raw materials testing, in-process testing, testing of container/closure system and stability testing.

Over the last years it has become evident to the Assessors of the Quality/CMC part of MAA dossiers that it is not only relevant to assess the actual specifications but equally important to understand how the controls presented in the dossier are linked to the overall product control strategy. The overall control strategy for a given product also includes providing an understanding of the consequence, if an acceptance criterion is not met or if the result is out-of-trend even though the acceptance criterion is met, and how the required Quality Control System according to GMP will handle this. Currently, there seems to be an imbalance between the information provided in the dossier for review and the actual (huge amount of) data from controls and measurements performed during development and manufacture of a medicinal product. It is therefore desirable for the Quality/CMC Assessors that a general introduction/description of the overall control strategy and Quality Control System for a medicinal product is provided in the dossier to enable better understanding and dossier review.

Thomas Stangler (Sandoz) described specific challenges faced when CQAs and Critical Process Parameters (CPPs) were implemented. It was pointed out that the sequence of elements to be considered in biopharmaceutical development is:

- The establishment of a Quality Target Product Profile (QTPP);
- The determination of CQAs, linking quality attributes to clinical safety and efficacy;
- Process risk assessment, linking process parameters and critical material attributes to CQAs and defining CPPs;
- Definition of a design space (optional);
- Design and implementation of a control strategy using a risk assessment (e.g. by linking CQAs to process capability and detectability);
- Management of product life cycle, including continuous process verification (CPV) and continual improvement.

He considered that process considerations should be kept separate from the CQA assessment because the CQA impact on safety and efficacy is independent of process capability and process changes should not impact a quality attribute criticality.

The general concept proposed for quality attribute criticality assessment, which is also part of A-Mab case study, was described. The scoring impact, which is part of the determination of the criticality score, was considered as a good example of what regulators would like to see. Industry presented the dilemma of high uncertainties: what is more critical between high impact & low uncertainty (i.e. "I know it has an impact") and high uncertainty & and high impact ("It might have an impact")? An alternative approach was proposed, considering criticality as a continuum rather than a binary state: it was suggested that highest criticality should be put on high impact & low uncertainty. A continuum of criticality can also allow a selection of control measures (e.g. characterisation & comparability testing, IPC, specification) which commensurate with the quality attribute criticality.

To answer the question "What to control", the process capability to influence a given quality attribute needs to be considered in addition to the quality attribute criticality.

He presented an FMEA-based example for a process parameter risk assessment that reflects process capability, and builds up in an efficient and step wise approach along the development of the product. A corresponding classification of process parameters (see "A-Mab case study") was presented:

- CPP defined as the process parameter that must be maintained in a narrow range to ensure acceptable product quality.
- Well-controlled process parameters: although critical, the parameter is easily controlled in a meaningful range and is therefore of low risk.
- Key process parameter: process parameter that must be maintained in a narrow range to ensure process performance consistency and robustness.
- Non-key process parameter: easily controlled process parameter with no impact on quality and performance within wide ranges.

The final testing strategy (IPCs and specifications) depends on both the quality attribute criticality and process capability (with consideration of abundance), and must be chosen in the context of the overall control strategy in order to assure product quality.

Session 2 – Basis for setting acceptance criteria

Mats Welin (Medical Products Agency, Sweden) reminded the audience of the different sources of data to be taken into account when establishing acceptance criteria according to ICH Q6B:

- Data obtained from lots used in preclinical/ clinical studies;
- Data from lots used for demonstration of manufacturing consistency;
- Data from stability studies and relevant development data.

The following dilemma was pointed out: how can we find acceptance criteria that do not exclude “good batches” because of normal variation but that can still pick up “bad” ones resulting from deviations in manufacturing process, starting material, etc?

Clinical qualification is considered the most important aspect when setting acceptance criteria. For critical attributes it is considered that the acceptance criteria should not be wider than what has been qualified to yield a safe and efficacious product. One key issue is the fact that often few batches are used in the pivotal clinical trials and those may not cover the full span of normal process variability. It was deemed acceptable to use data from similar processes (platforms), from non-clinical information and clinical trials in earlier stages. Some considerations to be taken into account in the justification of acceptance criteria were what prior knowledge from platforms and early phases of clinical trials can be used as not all clinical trials look at relevant parameters (e.g. immunogenicity). Dose finding studies can be useful in justifying limits as, for example, the absolute content of an impurity in a high dose study can be used to support a higher level than what has actually been used in the recommended dosage. Non-clinical data can be useful to support certain acceptance criteria and in classification if a form is fully biologically active or not, but has obvious limitations to predict, for example, immunogenicity in humans. Drift, for example in glycosylation or charge pattern, where a form already exposed to humans is increasing or decreasing, may be less critical than the appearance of a totally new form.

Acceptance criteria for non-critical attributes can be based on process capability allowing wider limits than what has been used in clinical trials.

It was outlined that validation should show that a commercial process results in a product falling within clinically qualified limits. Reference to acceptance criteria applied in the clinical trials is not sufficient to justify commercial acceptance criteria as the former may be much wider.

Some issues in relation to the use of statistics and stability in justifying acceptance criteria were raised. It was pointed out that it was not considered appropriate to add method variability as determined in analytical method validation to the variation seen in batch results as this variability is already included in the batch results and therefore will be counted twice. Stability data obviously need to be taken into account to set release limits that will assure a clinically qualified level during the whole shelf-life. Age of material when used in clinical trials can also be used in justification of acceptance criteria, as the actual level when applied in patients may be different from the results at release.

It was pointed out that specifications are only one part of the control strategy. Based on this, a question was raised as to whether or not it would be possible to separate the two key aspects in setting acceptance criteria- clinical justification and consistency- and to base the regulatory requirements on the clinically qualified levels and to handle consistency (process capability) through the company's Pharmaceutical Quality System (PQS) (for example alert/ action levels) where the principles are described in the dossier (for example what are the principles applied in the assignment of alert/action limits and what kind of action is triggered if results are outside these limits) to assure regulators that things are under control. If a result outside the normal trend was seen, a root cause analysis should be performed and depending on its outcome a batch may or may not be released even

if within the clinically qualified level of that particular attribute. Despite adding descriptions of certain parts of the PQS in the file, the final approval of this will always rest with the inspectors.

Brian Withers (Abbott) brought up a number of points for discussion from an industry perspective. Considerations include the questions of how to account for variability, how clinical experience can be limited and how the linkage of quality attributes to clinical outcomes can be difficult. How and to what extent “other data” from, for example prior knowledge, can be used and, very importantly, how can specifications be adopted in a way that life cycle improvements are not inhibited.

He posed the question “are we too preoccupied with demonstrating consistency with what has been produced during development”. The proposition was to be more focused on answering the question “what is the acceptable level of variability for an attribute that ensures safety and efficacy of the product”. Limits for quality attributes can then be set in a way that allows for making future process changes. Two examples were presented, the first one based on a literature example concerning the assessment of glycoforms where it could be demonstrated that there was no impact on pharmacokinetics within wide range of glycoform profiles. It was argued that to set specification limits based on consistency would inhibit the ability to make changes in cell culture to improve yields in a post-approval setting. The second example was based on example 3 from ICH Q11 which showed the impact of specification limits on the definition of a design space and how the design space would be limited if specifications were set based on consistency alone.

Industry emphasised that the use of data from pilot scale, prior knowledge, and earlier processes as well as data on batches used in phase 2 studies can all be used to support determining appropriate ranges for specification. It was emphasised that batch analysis data can be limited at scale – validation batches (3 lots?) can demonstrate a level of consistency, but it was questioned if they give a sufficient measure of future variability. Clinical experience is not limited to phase 3 data, and often phase 2 data has been generated with higher doses and this should prove usable in supporting specification limits. The use of *in vitro* assessments was exemplified where a monoclonal antibody shows significant deamidation following administration. In this case it was argued that it would never be necessary to set limits based on consistency, since the safety and efficacy profile would be based on the patient being exposed to the deamidated form of the molecule. It was also pointed out that post-approval assessments based on risk management plans, or phase 4 clinical studies provide a source of information that support a life cycle approach to specifications.

A point of discussion related to pharmacopoeia requirements was under what circumstances it would be necessary to go beyond the standards set by the Ph.Eur.

Session 3 – Statistical considerations in setting acceptance criteria

Basic statistical tools for setting up acceptance criteria such as reference intervals and tolerance intervals were presented by **Kay Martin Hanschmann (Paul Ehrlich Institute, Germany)** and **Enda Moran (Pfizer)**.

It should be noted, that these tools are applicable for analysis on process data only, and cannot be applied on data from clinical verification.

Reference intervals, which can easily be described by the 1-2-3-sigma rule, include a certain amount of data (for example mean $\pm$ 2 Standard Deviations (SD) covers about 95% of the data, mean $\pm$ 3SD covers more than 99% of the data), provided that the data is normally distributed. If the data is not normally distributed (for example follow a skewed distribution), a transformation might be applied. It is important to reliably estimate the mean and SD.

Tolerance intervals correspond to intervals that cover percentiles of the population with a certain probability. They can be either parametric or non-parametric. A tolerance interval is more reliable with a sufficient amount of validation data. Dynamic tolerance intervals are not recommended: they can be set up for few determinations and narrow with growing amount of information, but a slight trend or increasing variability would gradually enlarge them. Thus a trend could be remarked too late.

In some cases a two-step approach could also be envisaged: 1) to set up early validation limits; 2) to perform a re-validation after additional data has been obtained. This is relevant for example if an early preliminary specification shall be implemented, which shall be confirmed later when a sufficient amount of data is available.

Both, reference and tolerance intervals can be set up after a validation phase which should reliably estimate the parameters of interest. Within specification intervals, additional **warning limits** might be useful to be able to early detect the beginning of negative/positive trends, when for example these warning limits are exceeded more frequently.

Specifications should exclude the critical data range, where it is known e.g. from clinical data that sub-potency, safety issues, or other unwanted quality characteristics might be linked to the measured parameter.

Process Performance Indexes (PPIs) were also mentioned (e.g. $\text{mean} \pm 3\text{SD} \times \text{Ppu}$). They have the advantage of being product specific since Ppu differs with the type of product (distance between the process mean and the upper specification limit scaled by process standard deviation). The use of PPI with a 6-sigma limit was not recommended.

The limitations of using **outlier tests** without having a broader view of the distribution of data was pointed out.

General problems that might arise with setting up acceptance criteria are a limited amount of data. Thus few homogenous values could result in a too narrow acceptance interval (risk of falsely rejected batches), whereas determinations with a high variability in the validation phase could result in too broad intervals including samples with undesired quality characteristics (risk of falsely released batches).

It was agreed that setting specifications cannot be based on mathematical techniques only: it's a **holistic approach** taking into account for example product and process knowledge, process variability, process capability to deliver a product within putative specifications limits, development history, analytical method variation, non-clinical and clinical experience. Statistical approaches should be used as supportive and there is no universal statistical tool as it is parameter- and product-dependent.

The importance of not having either too narrow intervals (risk of falsely rejected batches) or too wide intervals (risk of falsely released batches) was pointed out.

Industry questioned the need to change specification limits in reaction to any measure of process variations if it was demonstrated that these limits gave assurance that the product is safe and efficacious for the patient.

The problem of having a limited number of observations/data points was highlighted as this can lead to difficulties to calculate a reliable estimate of a SD, to assess distribution or process stability.

Session 4 – How and where to control and what to put in the file

Kowid Ho (Afssaps, France) provided the regulators view. ICH Q10 defines **control strategy as a planned set of controls**, derived from current product and process understanding that assures process performance and product quality.

Quality attributes can be controlled directly at relevant step(s) or indirectly, for example by controlling surrogate quality attribute(s) at an appropriate step or by controlling process parameters correlated to the given quality attribute (parametric control). Control of process parameters can also be performed directly, indirectly (for example correlated to other parameters), or using procedural controls.

The different types of quantitative “limits” are described in ICH Q6B:

- Acceptance criteria for drug product, drug substance or intermediates. In case of an out-of-specification result, an investigation is triggered to determine the root cause, and may lead to the rejection of the batch if confirmed.
- Internal action limit triggers an action if the limit is exceeded, and may allow more flexibility as it is the responsibility of the manufacturer.

Monitoring and control can be performed routinely (for each run), periodically (at defined frequency and/or conditions such as skip lot testing) or occasionally (in specific situations such as evaluation/validation, characterisation, comparability), and can be facilitated by the use of Process Analytical Technology (PAT).

A test present in the specifications does not necessarily imply that it has to be performed for each batch: **alternatives to routine end-product testing** can be claimed, such as real-time release testing (RTRT) which ensures the quality of in-process and/or final product based on process data and is applicable to drug substance, drug product and intermediates. With RTRT it may be necessary to provide data on more than 3 validation batches traditionally requested in order to demonstrate good product and process understanding and it may also be necessary to run a given test during a certain period of time before dropping it.

A “validation approach”, corresponding to the demonstration of process robustness/capability (e.g. to remove impurities), could reduce the amount of data required in terms of controls: in such situation, process monitoring may be carried out without direct measurements of the quality attribute. If the demonstration is not sufficient, it is possible to use a combination of routine testing and “validation approach”.

As part of an “enhanced” approach, when considering for example a quality attribute “impurity formation”, if sufficient clearance capability can be demonstrated when operating within a design space, it may not be necessary to routinely test this quality attribute.

The **information to be provided in a MAA** was also discussed. A summary and justification of the control strategy (and its evolution during development), a justification of the drug substance and drug product specifications, including an explanation why certain attributes are not present in the specifications, should always be provided, irrespective of the approach followed (i.e. “traditional” and “enhanced”). For an enhanced approach, comprehensive information on the risk ranking/filtering tool used should also be part of the justification.

As part of the control strategy, if an action limit is reached, information on the actions to be triggered could be presented in the dossier and could include additional parameters that would normally not be controlled.

It is also important to present a detailed description of the manufacturing process and process controls, although reduced details could be accepted for an enhanced approach with a design space. In the case of a design space, a clear description of the steps covered by the design space(s) and a summary of the design space(s) should also be provided.

Information on process evaluation/validation is also important. Detailed results of in-process tests and batch analyses on consecutive batches should be provided. For an enhanced approach, this should include detailed information for example on design of experiments, interaction between CQA(s) and CPP(s), continuous process verification.

Karin Sewerin (MedImmune) emphasized that the specification is only a part of the overall control strategy. In the CTD submission for registration, every section (from manufacturing process development, process evaluation and batch analysis to characterisation, methods validation and stability program to regulatory requirements) is contributing by justifying what is critical and what is not, by providing the rationale for where in the process to control for a critical attribute as an IPC or as a specification.

CQAs can be controlled either in process by validation or by end-product testing on drug substance or drug product.

An example was provided using the oligosaccharide profile of an antibody. An initial criticality assessment would give the information of whether or not testing should be required. In case the oligosaccharide structure is a CQA based on impact on safety or efficacy and testing is required, can the testing be conducted as an IPC in lieu of end-product testing, as prior knowledge has demonstrated that, in this case, the glycoprofile is not altered during purification or storage?

Alert and action limits may be utilised for internal trending and be associated with an action for correction when exceeded without resulting in a rejection of the batch. The specification limits correspond to defining the limits for approval or rejection that has been agreed with the regulatory authority based on patient's safety and efficacy. Action limits performed as IPCs may also be associated with a retest at a later step in the process to confirm that the product quality is not altered and limits are met at the final stage.

Trending is a way of following process performance independent on whether the testing is measuring a critical attribute or not, and may therefore not be reported in the license application. It was pointed out that the regulatory specifications limits should not be tightened by default as the ranges agreed upon at the time of licensure were acceptable to provide a safe and efficacious product. However, deviation from the trend can indicate a problem and should be investigated.

Session Questions and discussions

Criticality was extensively discussed.

Industry proposed that if a criticality assessment shows that a quality attribute (for example oligosaccharide profile for a monoclonal antibody) is not a CQA, no routine monitoring of this attribute should be required. Regulators argued that the absence of monitoring could be an issue because it is then not possible to know whether this attribute goes beyond its normal variability. It was then proposed that only in cases where there is disagreement between the sponsor and the regulatory authority on the classification of a specific quality attribute to be critical or not, the quality attribute in question should be specifically mentioned in the file as being monitored as part of the PQS and action proposed what will happen if the internal limits are exceeded. Industry clarified that the fact that a non-CQA is not tested upon release or as IPC does not mean that it is not under control as part of the overall control strategy.

It was pointed out that this is important information to the assessor who then can trust that the quality attribute is under control. It was proposed by a regulator that a summary of the control strategy describing these issues could be useful and would reassure that the production is under control.

It was explained that “criticality” of attributes and “risk” are two distinct notions. CQAs could be classified as “high risk” or “low risk”, but it should always be demonstrated that they are under control. For high risk CQAs this would normally require a test with a registered limit while for the less risky but still critical attributes, a statement that the attributes are tested and handled with internal action/ alert limits would be sufficient.

The fact that a process change can unexpectedly impact on a quality attribute is a distinct issue because such change is intentional and should be supported, where relevant, by a comparability exercise where CQAs/non-CQAs, CPPs/non-CPPs are evaluated.

In relation to the definition of CQAs/non-CQAs, Industry highlighted the following issue: how does one show that an attribute is non-critical and how can one get full knowledge of what will be the impact for example on *in vivo* performance and safety? The level of knowledge will differ from product to product. For the time being the level of knowledge for monoclonal antibodies is quite advanced while the knowledge gap is more pronounced for vaccines and plasma-derived products.

It was once again reiterated that specifications alone do not guarantee the quality of the product; they are only one part of the overall control strategy designed to ensure product quality and consistency.

Consistency vs clinical qualification According to ICH Q6B acceptance criteria should be based on clinical qualification, results from batch analysis and stability studies. Consistency is important to show that the process is under control but it was pointed out, both by regulators and industry, that the clinical qualification should be the main basis for setting acceptance criteria for CQAs. The question was raised if it is possible to split the aspects of consistency and clinical qualification in two where the registered acceptance criteria would be set based on clinical qualification and consistency is handled by the company’s PQS with internal action/alert limits. As mentioned above, a summary of the applicant’s system to handle these could then be valuable for the assessor to assure that not only the attributes are within levels that will assure safety and efficacy but also the process is under control, yielding a reproducible product. No clear conclusion was reached but the question deserves more discussion.

It was pointed out by industry that process consistency and performance do not necessarily have to be verified by testing on drug product. Control and verification of consistency can also be achieved by IPC and/or demonstrated by process validation. Currently it is accepted that DNA and Protein A are validated out while this is not accepted for other attributes such as aggregates even if the manufacturing process was shown to be robust in the removal of these and options to control the process rather than the product could be a topic for further discussions.

It was mentioned that tools such as multivariate analysis could be useful in assessing outliers. It was also pointed out that it could be valuable to include also physicians in the discussion of setting acceptance criteria to stress the importance of effect on safety and efficacy.

How to justify acceptance criteria with few clinical batches

The difficulty to set clinically justified limits when only few batches have been used and these batches do not mirror the normal expected variation was raised. It was clarified by a regulator that results from studies with higher doses could be useful in the justification of specifications- the actual amount exposed to a patient could be transformed into an equivalence at the chosen dosage level. The power of the study to show adverse reactions needs however to be taken into account (for example number of patients, aspects monitored).

It was suggested by a regulator it could be acceptable to initially have “wide” specification limits which have been clinically justified, with a commitment to review them and tighten them if possible, once a sufficient number of additional batches has been produced. The industry perspective was that trending of process performance should be conducted to assess consistency of manufacturing and that tightening of the acceptance criteria would not be a necessary consequence.

Outcome of the workshop

Shared views

- Specification is only one part of the control strategy- other parts contribute and should be considered in the setting of specifications.
- Clinical justification is the most important factor when setting acceptance criteria for critical attributes. The clinical justification should mainly be based on data from phase 3 studies, but information from relevant preclinical data and earlier clinical studies can be supportive. However, it is important to consider the relevance of these studies for the claim made.
- Process capability and detectability do not influence the classification of CQAs.
- Selection of tests for setting the final specification is influenced by criticality, process capability and detectability.
 - Data from small-scale experiments may be used to assess process capability.
- Setting specifications cannot be based on mathematical techniques only: it is a holistic approach. Statistical approaches should be used as supportive and there is no universal statistical tool as it is parameter- and product-dependent.
- If it is agreed between regulators and industry that a particular attribute can be considered as non-critical there is no need to include a test for this in the file (or this can be handled internally by the company within the PQS)

Issues where more discussion is needed to reach agreement

- Classification of non-CQAs and its consequence on what goes into the file/ specification.
- Consider classification of high-risk and low-risk CQAs which may be treated differently in the file, changes handled through variation vs internal (shared) protocols/PQS
- It was recognised from both regulators and industry that there is a need for standardised terminology and use of ICH nomenclature when present. There might be a need for additional terms such as well-controlled process parameters, key PP, non-key PP and understanding of how this impacts the control strategy.
- CQAs should normally be clinically qualified, which may be difficult for certain impurities. The handling and need for a rational and justification for these needs to be made more clear.
- ICH Q6B indicates that both clinical qualification and consistency should be considered when setting acceptance criteria. Is it possible to handle these separately- regulatory requirements based on clinical qualification and consistency handled internally through the PQS? If so what should be communicated in the file?
 - If it has been shown that the product is safe and efficacious within certain limits, why is there a need to tighten limits based on process capability?
- How to use prior knowledge from *in vivo* information to justify specifications? (for example on complete deamidation of a monoclonal antibody after injection).
- In which situations are the tests and limits of the Ph.Eur. not sufficient for justifying a specification?
- Today it is accepted that for example DNA and Protein A are validated out and that there is no need for routine testing. Can this be expanded to other attributes (for example product-related substances/impurities) where it has been shown that the process can robustly remove unwanted forms?
- A need was identified for the selection of statistical approaches to be applied for certain conditions and when to use what statistical approach.

Next step: How to proceed?

It is proposed that based on the topics identified above, (a) focus group(s) are formed with members from both industry and BWP to further discuss the issues and to try to reach a harmonised view. Their

work could then be presented for example at a relevant CMC forum to stimulate a more global discussion including industry and regulators also from other regions.