Clinical qualification of specifications
- a Regulator’s view

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Disclaimer: The opinions expressed are my own and do not necessarily represent those of the MPA or EMA
What is a Specification?

Definition according to ICH:

• A specification is
  – a list of tests
  – references to analytical procedures
  – appropriate acceptance criteria

• “Specifications establish the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use.”
Fundamentals ICH Q6B

“Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency and data from stability studies, and relevant development data.”

“Specifications should be based on data obtained for lots used in pre-clinical and clinical studies. The quality of the material made at commercial scale should be representative of the lots used in preclinical and clinical studies.”
Regulatory concerns

**Outcome EMA- industry workshop 2011:** Specifications should ensure that the product is safe and efficacious and representative of batches used in clinical trials.

Clinical qualification are considered the most important aspect when setting the acceptance criteria.

- Acceptance criteria applied for critical attributes should normally not be wider than what has been clinically qualified.
  - n.b. not necessarily restricted to levels used in clinical trials
- Acceptance criteria for non-critical attributes can be based on process capability allowing wider limits than what have been used in the clinical trials
ICH Q8

• "Adoption of the principles in this guideline can support the justification of alternative approaches to the setting of specification attributes and acceptance criteria as described in Q6A and Q6B."

• My interpretation: You can build your control strategy differently (RTRT, IPCs vs batch analysis no test for nonCQAs, no routine test if acceptable levels always found- DNA, HCPs- etc.) taking Q8 principles into account **BUT** there is no opening saying that using QbD you don´t have to justify that your maximally allowed levels are clinically justified.
Problem statement

• Two aspects for discussion:
  – Which attributes should be tested for?
  – What is an appropriate acceptance limit?

• Attribute selection is related to criticality-
  – out of scope for this discussion

• Setting acceptance limits is linked to clinical safety and efficacy
  – Each commercial batch should be representative for what has been successfully used in clinical trials or be within levels qualified by other means.
    • N.b actual levels found, not limits applied in Phase 3 studies.
Nature of test vs principles of setting acceptance criteria

Depending on the nature of the test, principles of setting acceptance limits differ

• Compendial (e.g. appearance, subvisible particles, endotoxins, bioburden/sterility, container closure integrity, extractable volume) - Follow published limits

• Nonproduct specific (e.g. clarity, colour, identity, content of excipients, osmolality, pH) - acceptance criteria set based on product design

• Product specific tests (e.g. purity, potency, glycosylation pattern) Primarily based on clinical justification.
Principles in setting spec´s

- What should be clinically qualified is what may meet the patient during the shelf life of the product, i.e. DP shelf life limits.

- In case of DP instability issues, tighter DP release limits may need to be set.

- In order to meet these, an appropriate shelf life limit of the DS should be set.

- In finally, the DS release limit should be set to fulfil the DS shelf life limit in order to fulfil the DP release and in the end the DP shelf life limit.

- As a consequence: The DS release limit can be wider than experience from batch testing provided that fulfilment of the DP end of shelf life limit can be assured.

- For attributes not tested in DP spec´s, the limits in DS need to be justified.
Principles in setting spec’s

Figure 1: Degradation during Shelf-Life and Manufacture

- \( \beta_{DS} \): average DS degradation rate
- \( \beta_{DP} \): average DP degradation rate

Critical Quality Attribute

DS manufacture \( \rightarrow \) DS storage

- DS release specification
- DS shelf-life specification

DP manufacture \( \rightarrow \) DP storage

- DP release specification
- DP shelf-life specification

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General experience

• Questions on spec´s frequently asked (Top 3 topic)
• Spec´s proposed/revised to avoid redundancies
  – Less tests at the DS/DP, more IPC, test where most relevant
• IPC with different outcome (action limit/rejection limit)
• Deletion of tests due to long experience of fulfilling the specs
  – Most relevant for products on the market
• Statistics used in justification
Common issues identified in applications

- Making use of statistical tools (e.g. tolerance limits) even with few observations leading to wide acceptance criteria (±5-6 SDs) with outer boundaries far from what has been exposed to patients.
  - TI’s are absolutely fine if the resulting range can be clinically justified by clinical product specific/ relevant platform experience. But they rarely can.
- Addition of analytical variability even if this is included in batch data.
- Adding extra safety margins due to limited number of results
- Not a single word on how the levels can be considered clinically justified
- Very often a combination of these.
Real life example

Heavy Chain and Light Chain

• “Heavy chain and light chain by CGE Reducing is one of the purity tests for XXX drug product performed at release and during stability. The range of heavy chain and light chain is 97.8 – 99.5% for 14 drug product lots.

<table>
<thead>
<tr>
<th>Mean (Heavy Chain and Light Chain)</th>
<th>SD (Heavy Chain and Light Chain)</th>
<th>Tolerance Interval (Heavy Chain and Light Chain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>98.3%</td>
<td>0.50%</td>
<td>Lower 96.7%  NA</td>
</tr>
</tbody>
</table>

• Since there is a limited data set and limited experience in the commercial environment, the acceptance criterion for heavy chain and light chain at release is ≥ 95.0%.”

• Clinical batch range 98.1-99.5%. No clinical justification of limit
For monomeric IgG, the lower tolerance limit at the drug substance end of shelf life is \( \geq 97.75\% \). This tolerance limit supports the proposed acceptance criterion of \( \geq 96.0\% \) for drug product release. Taking into account the expected decrease in monomeric IgG over 2 years from the date of manufacture yields an adjusted lower tolerance limit of \( \geq 97.35\% \). This tolerance limit and the limited data set support the proposed acceptance criterion of \( \geq 95.0\% \) at the end of drug product shelf life.

Clinical batches at release \( \geq 98.7\% \) monomers, following 36 M storage all results \( \geq 98.3\% \)
Dilemma

• How can we find acceptance criteria that do not exclude ”good” batches because of normal variation but still is able to pick up outliers that are results of deviations in manufacturing process, starting material etc?

• Clinical justification of limits necessary to meet process capability may be challenging as only few batches normally is used in clinical trials
  – PRIME/ Breakthrough therapies

• If limits are considered clinically justified, is there a need to tighten when more experience is gained?

• Is it justified to have limits which are not clinically justified for any product? Would PRIME etc call for a different risk benefit- i.e residual uncertainty/risk from specification settings is overruled by clinical need?
Considerations

• What prior knowledge (e.g. platform knowledge from a particular IgG subtype) can be used in claiming clinical justification?
  • Not all clinical studies look at relevant parameters (e.g. immunogenicity) to verify if certain product related forms gives rise to antibody formation or not.
  • Consider indication and dosage
  • Consider route of administration- iv experience may not always be easily transferred into sc or im administrations and vice versa.

• Dose finding studies can be useful- even if the content of a particular impurity expressed in % may be below the proposed limit, the actual exposure should be accounted for (e.g. results from 2x dose studies may justify a higher % than used in the studies of the chosen dosage)
  • In case relevant analyses in relation to safety issues have been performed using higher doses than applied for this is a powerful tool (e.g. immunogenicity, preferably more than one dose)

• Structure effect studies can be useful in justifying limits.
  • Certain attributes clearly related to safety issues, others only efficacy.
  • Activity of a certain attribute may be used in calculation of impact on overall efficacy.
Considerations cont.

• Non-clinical data could be useful in justifying acceptance criteria but normally the concern in relation to impurities in biotech products relates to immunogenicity rather than toxicity and the value of non-clinical data are therefore limited. Could be used for other aspects though.

• Use info gained in establishing criticality. In vitro incubation at 37°C in serum may be used to predict the levels of a particular form following injection. If rapid turn-over- less criticality. Compare to native ab´s.

• Drift in e.g. glycosylation or charge pattern where a form already exposed to humans increases or decreases may be less critical than the appearance of a completely new form.
Take home messages

- Make use of the sections on justification of specification 3.2.S.4.5 and 3.2.P.5.6 to explain why you consider the specifications (acceptance criteria, range of attributes tested) justified to assure a product which is representative for batches used in clinical trials on which the conclusion of safety and efficacy is based.

- Frequent experience- purity data ≥98.5 % in clinical batches, proposed acceptance limit 95 % with no further comments. May or may not be of importance but not up to the regulator to guess this- justification needed.
And more…

- Statistics alone will not be accepted as a reason for having much wider limits than what has been qualified.

- Start with the end- DP shelf life limit and work from there. Instabilities in storage or manufacture should be compensated for.
Thank you!