



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Validating the extrapolation concept – methodological considerations

Andrew Thomson

Extrapolation Workshop Session 5

Presented by Andrew Thomson on 18 May 2016
Statistician: Office of Biostatistics & Methodology Support, EMA

An agency of the European Union





What is envisaged by validation?

Study or studies that answer whether specific assumptions are valid, and/or are designed to provide data that address key uncertainties, that are not addressed by the other studies in the extrapolation plan.

It is a study that is part of the extrapolation plan.

What this data should look like is a case-by-case basis, and may change through development as knowledge .

We know the answer is not 'a fully-powered efficacy study'.

Focus on assumptions and uncertainties.



End of Adult Phase I

- No real information on PK-PD.
- Not going to be possible to extrapolate (full paediatric development).
- But mindful that further PK / PD data will be forthcoming in Phase II.
- Reasonable to start planning for the possibility, even if *right now* a full development would be required.



End of Adult Phase II

- Better understanding of the PK / PD relationship in adults.
- May still require an efficacy study.
- Approaches such as the scepticism factor might define how you can define an appropriate level of alpha in principle.
- Controlled efficacy data still likely to be the main requirement at this stage.

End of Adult Phase III

- More knowledge about PK-PD-Efficacy relationship.
- May be able to incorporate this into the design of the paediatric studies.
- May wish to alter the design of the studies accordingly.
- At all stages, important to detail the assumptions being made, and the uncertainties that are inherent in the process:
 - Uncertainties in the model;
 - Uncertainties in the data.
- And potentially further paediatric data, e.g. in other indications.



Assumptions do not need to lead to uncertainties

Example Assumption. Model assumes Parameter x takes the value 3 in the model.

What data is used to decide on this number? Where does it come from? It's not enough to say 'well its what everybody has always done'; where is the data?

Does it matter? What if it is 4, does the model output change? 5? 6?

How likely are these different values – i.e. is there any data for that?

Can we actually measure this parameter in real life?



Strong assumptions may not always mean that controlled efficacy data are required

Assumption that PD marker in PK/PD model defining 'response' is a good marker of relevant clinical efficacy:

It may be well known: see Concept paper on an addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2) to address paediatric-specific clinical data requirements

It may be the PD marker is well-developed in adults but not children. This may be OK, it may not.

So what do we need? Controlled data? Uncontrolled data? Prospective registry / relying on EHRs etc.

Scientific judgement putting together PK – PD - Efficacy



Uncertainties

If we do need some form of controlled data, to provide reassurance that the observed PK/PD similarity translates across into efficacy, as we do have a lot of uncertainty there, how much efficacy do we need? What does the study look like?

What sort of efficacy endpoint do we need, assuming we already have some PK / PD data?

Should we take into account the strength of evidence generated in adults? (e.g. if the effect is very impressive, large treatment effect $p < 0.0001$ can we be more relaxed about extrapolating this). This is a measurement of the uncertainty in the source data.



What design features can we alter?

Can we summarise information in the form of Bayesian priors that make sense to clinicians? Can we use these without Type 1 Error becoming too large?

Can we use a principled quantitative method for defining how much data we need? e.g. changing the p-value in a non-arbitrary fashion with a scepticism factor.

Can we think about a combined approach with say $p < 0.2$ for a traditional frequentist analysis, but $p < 0.05$ under the Bayesian framework?

Should we just widen the NI margin (by how much? How?), or use the usual efficacy endpoints but on a different scale? e.g. continuous measurements usually have more power than dichotomised versions of them.

What is methodologically important

We know we are reducing the data requirements, which leads to changes in design.

It is easier to understand if we only change one of these requirements so if possible pick only one aspect of the design to alter.

e.g. more challenging to interpret a study run at 5% alpha one-sided with a wider than usual non-inferiority margin.

Whatever chosen, criteria for success should be clearly defined *a priori*.

Ideally, there should be a plan as to what should happen next if the study is not considered successful.



What features should the study have, regardless of the design modifications made?

When an efficacy study is run, it should at the start:

Be feasible;

Answer a relevant scientific question of interest;

Likely lead to different regulatory decisions depending on the results;

Aim is to minimise any unplanned modifications after the start of the study, by developing the protocol as fully as possible in advance (whilst recognising clinical development can still throw up unforeseen challenges).



Conclusions

What is known in the source population regarding PK-PD-Efficacy changes over time, and thus the confirmation / validation study may change over time as well.

Summarise the assumptions in any model, test them, and see if these assumptions lead to uncertainties in the model outputs. If so, work out how to best address these.

Summarise all the other uncertainties, mindful that there will inevitably some residual ones left at the end.

Identify which ones are critical and need to be addressed pre-licensure.

Design study / studies that address these ones, in as principled fashion as possible, appropriately using as much data generated to date as possible.



Thank you for your attention

Further information

andrew.thomson@ema.europa.eu

European Medicines Agency

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom

Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555

Send a question via our website www.ema.europa.eu/contact

Follow us on  **@EMA_News**