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New Frontiers in Inhalation Technology

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Globally Divergent Regulatory Strategies for OIPs?

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Note

I am a consultant. Present and past clients include WHO, regulatory agencies, USP, and companies (Inno+Gx). Former regulator, managed the work that led to the 2009 guideline of therapeutic equivalence for OIPs in EU.

This presentation reflects my own opinion and impressions, and no support (financial or otherwise) has been received.

This presentation is not a recap or an overview of existing guidelines.

My field of work is typically regulatory science and M5 (clinical efficacy and safety). I know very little about devices and CMC.
The good news

US, EU and Canada, Japan etc. are totally aligned.

You will be granted an approval if your product is safe, efficaceous and of adequate quality. Period.
Harmonization?

It is spelled “Harmonisation”.
EMA/FDA 2004

Regulators kicked off a project centered on parallel scientific advice with EU and FDA.

“The expected advantages from such interactions are increased dialogue between agencies and sponsors from the beginning of the lifecycle of a new product, a deeper understanding of the bases of regulatory decisions, and the opportunity to optimize product development and avoid unnecessary testing replication or unnecessary diverse testing methodologies.”
But...

“The goals for Parallel Scientific Advice procedures should focus on sharing information and perspectives, rather than specific harmonization of study or regulatory requirements, although if harmonization is achieved, that could be a beneficial outcome. (…) Each agency will provide their independent advice to the sponsor ”
April 2017

EMA/309801/2017

GENERAL PRINCIPLES
EMA-FDA PARALLEL SCIENTIFIC ADVICE
(HUMAN MEDICINAL PRODUCTS)
“Each agency will provide the sponsor its independent advice on the questions posed during the PSA process, according to usual procedures and timelines. Sponsors should neither expect to receive similar recommendations from the two agencies regarding drug development issues nor expect to receive similar agency decisions regarding marketing applications that have undergone PSA. However, both agencies will strive to provide PSA responses that are convergent.”
Overview of news on the regulatory scene for innovators drugs.
Asthma and COPD

Nothing.

For an innovator it is entirely feasible to conduct a study that is compliant with both FDA and EMA expectations.
Example of lack of harmonization
-not obvious from guidance

US: Companies are asked to develop and study mono's when seeking approval for combos.
Other areas

Pulmonary DD is receiving focus for pain management, migraine, nausea, Parkinson, metabolic diseases, and much more.

From an M5-perspective these applications are handled by the GLs in their respective therapeutic areas. I do not see much need for GLs that separate OIPs from other routes of administration.

E-cigs: Infection causing headaches.
Handling = a future ICH task?

It was never a task of ICH to harmonize clinical requirements in specific therapeutic areas.

Harmonization of device handling would fall within the traditions of ICH.

...and I know it has been brought up!
What TE/BE OIPs have in common with Biosimilars.

Extreme interest from generic companies.

Numerous conferences with regulatory presence where science has been secondary to certain other interests, in my opinion.

This has put regulators in a very difficult situation. The information that companies put into the public domain is often very heavily biased.
The generics scene is where it happens.

Several blockbusters expired or are about to expire. Several innovator companies are looking to turn generic, more or less publicly.

“If you can develop an innovator product and have it approved by FDA+EMA, surely it will be easy to copy the competitor's topseller. And the generics companies are failing.”
In actuality

9 out of 10 developments are failing, and “innovator companies” are not faring any bit better than generic companies in that regard.

Developments fail on the similarity, not on the variability.
“Developments fail on the similarity, not on the variability.”

Means:

This is not about e.g. training or controlling error variance.

It is entirely about actually matching two formulations. We can call it IVIVC. No one has (had) good options for defining an in vitro metric which correlated well with in vivo outcome.
A great paper which has been widely misunderstood or misused

Validation of a General *In Vitro* Approach for Prediction of Total Lung Deposition in Healthy Adults for Pharmaceutical Inhalation Products

Bo Olsson, PhD, Lars Borgström, PhD, Hans Lundbäck, PhD, and Mårten Svensson, PhD
What Olsson et al. published
Industry interpretation - completely harmonized.

Two formulations displaying a match in vitro with the appropriate cast/setup/CRO etc. must translate into a match in vivo. Use this approach to screen for matches and select candidate formulations.
= Industry saw a straight line without error bars.

And here's the thing: They still do!
Why is this an issue of practical importance?

EU and FDA both require PK-studies with classical designs. 90% Confidence intervals for T/R to be within 80.00 % - 125.00 %
Power in a 222BE trial, single API. (chance of showing BE if the assumptions about variability and match are correct)

Blue: T/R=0.95, CV=30%. At N=52 power is 90%.
Red: T/R=0.90, CV=30%. At N=52 power is 65%! N>100 needed for 90% power.
If we are just 5% wrong...

...about our assumptions about similarity then we will easily pick a sample size that in reality translates into a futile (unethical?) study.

If we have, say, a perfect match in vitro, are we then 'at any level' sure there is not a true 10% or 20% difference??

No, not at all.
Simply stated

We cannot use any known in vitro measure for screening or selection of candidate matching formulations with any useful level of certainty. It is not due to the lack of IVIVC per se, but due to the uncertainty associated with the existing IVIVC.
Please get me right

I think the paper is great.

I am not in any way criticizing it. I am, however, criticizing the way the industry has interpreted it. Those error bars are real and their magnitude is way, way too large for any predictions of outcome when we study equivalence.

This issue is a mighty show-stopper in both EU and US. Bluntly stated, we don't need harmonization as long as companies are continuing this practice.
Another regulatory issue
Coming to an innovator company near you!

There has always been quite a bit of flexibility wrt. to regulatory acceptance of deviations from guidelines for innovator companies.

E.g. in terms of population selection, treatment duration, endpoint choice(s), statistical approach etc.

Such flexibility does not exist for bioequivalence.
Another regulatory issue

Around ~2002 regulators opened up for widening the BE limits in BE studies generally for crossovers. The idea was that a drug with high intra-subject variance would not be problematic (as a definition) hence widened acceptance range would be safe.
Conceptually: Acceptance limits versus CV

US approach is similar but not identical.
Those HVDP for which a wider difference in $C_{\text{max}}$ is considered clinically irrelevant based on a sound clinical justification can be assessed with a widened acceptance range. If this is the case the acceptance criteria for $C_{\text{max}}$ can be widened to a maximum of $69.84 - 143.19\%$. For the acceptance interval to be widened the bioequivalence study must be of a replicate design where it has been demonstrated that the within-subject variability for $C_{\text{max}}$ of the reference compound in the study is $>30\%$. The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers. The request for widened interval must be prospectively specified in the protocol.

a. Scaling needs to be qualified in the same study as the one where scaling is applied.

b. Scaling needs three periods.

No flexibility. Generic companies get it 100% right every time. Originator companies don't always.
An example of a harmonized requirement, which is sometimes causing trouble.

Approval of a 505(j) “Generic” in the US requires a US-sourced reference product. Approval of a 10.1/2 product “Generic” in EU requires an EU-sourced reference product. Even if a release officer from the originator has confirmed they are identical and produced at a single site globally.

Again:
Generic companies get it right without discussion. Innovator companies are slowly learning it.
The difference between FDA and EU in a nutshell

EU: Stepwise approach, extrapolation. Hybrids (no substitution).
Pivotal evidence is generated by in vitro data or PK or PD. Few equivalence tests for the approval.

Pivotal evidence is generated by in vitro data and PK and PD.
About ~50 tests which all need to show BE. (Effective number of independent tests may be lower, but it is not known why/how/how much).
Inconceivable - simply not realistic.
FDA example (assuming independence)

Fluticasone propionate, Salmeterol xinafoate
36 in vitro tests.
12 PK tests.
2 PD tests.

If we want a 80% chance of success, then each test need a statistical power of 99.7%.
Sample sizes get astronomical.

Joker:
No easy way to calculate sample size for the in vitro part.
And remember: BE is a different beast in Europe

US: “The term “bioavailability” means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.”

EU: “‘generic medicinal product’ shall mean a medicinal product (...) whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.” (…) “In bioequivalence studies, the plasma concentration time curve is generally used to assess the rate and extent of absorption.”

A comparative PD trial may be called BE in the US but is not a BE trial in EU.
Message from EMA

Concept papers on orally inhaled products EMA

Two OIP concept papers have been published 22/03/2017 and can be found on the EMA external website.

End of consultation (comments deadline) 30/06/2017: opportunity to influence the revised guidelines.


And a word of warning

CROs globally are quickly adapting to the need for PK-evaluation of OIPs. LLOQs of < 1pg/mL are needed.
I have now seen several cases of CROs not being able to deliver A+P at those levels. Even in North America. Even in EU.
Solution: Manual integration of QCs and calibrators in LC-MS/MS

Note: Manual integration US vs. EU (open label)
Conclusions

- Approval principles are not entirely harmonized.
- Parallel scientific advice does not ensure harmonized approvals.
- Handling is a relevant ICH topic.
- 9 out of 10 developments are headed for failure.
- IVIVC models exist, but their variabilities are much too high to allow predictions when we talk BE.
- EMA guidelines are being revised and you can help!

Harmonization is not the big issue.
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- now enjoy your covfefe break.