Does the Estimand Framework Add Value to Clinical Pharmacology Trials?

YES!

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A Walk Through the Thinking Process

of ICH E9(R1)[1,2] with
a bioequivalence (BE) case study[3]

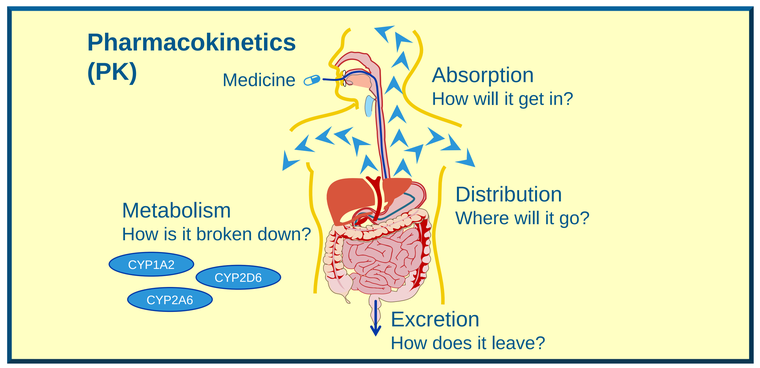
Step 1. Therapeutic Setting and Intent of Treatment Determining a Trial Objective

Pirfenidone: an oral anti-fibrotic agent used to treat serious condition of idiopathic pulmonary fibrosis with side effects of nausea, vomiting and rash (poor tolerability)

New formulation: film coated 801 mg tablet ? ≈ **Reference:** 3x267 mg capsules

Intent of new formulation: convenience of 1 tablet rather than 3 capsules three times per day (similar tolerability)

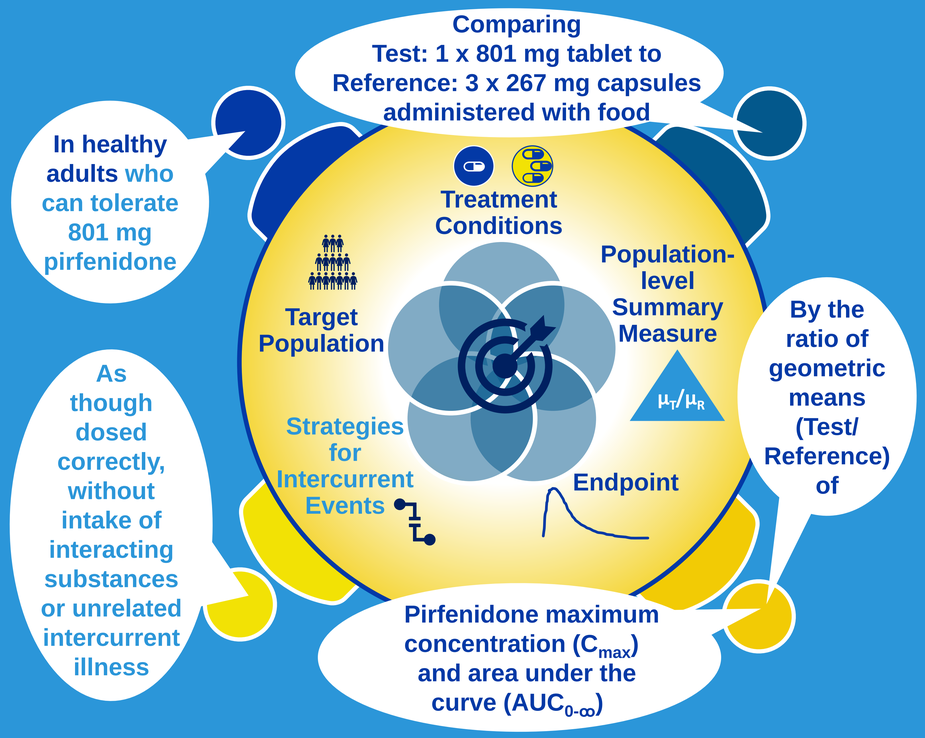
Objective: establish equivalence in the rate and extent of absorption of pirfenidone



Step 2. Identify Intercurrent Events / Step 3. Discuss Strategies to Address Intercurrent Events

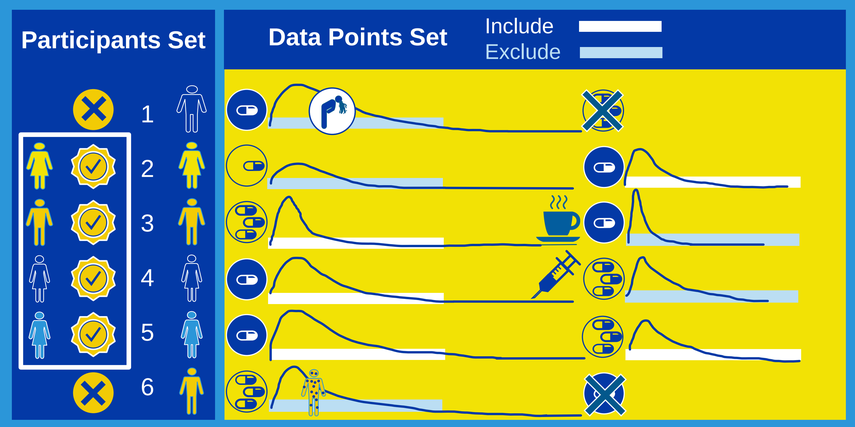
Step 2. Identify Intercurrent Events	Step 3. Discuss Strategies to Address Intercurrent Events
Discontinue due to any tolerability issue (vomiting or rash)	Principal Stratum: adults who can tolerate pirfenidone (dosed with food)
Incomplete dose due to dosing error or tummy bug (vomiting or diarrhoea)	Hypothetical: had the full dose been taken, and without illness impacting absorption
Dosing deviation (e.g. takes drug with hot drink)	Hypothetical: had the drug been taken as directed (with cold water) without impacting dissolution
Interacting drugs or substances	Hypothetical: had the drug been taken without interacting substances

Step 4. Construct the Estimand



Step 5. Align Choices on Trial Design, Data Collection and Method of Estimation

- 2x2 Cross-over with sufficient washout
- Healthy subjects without use of interacting substances
- Good study conduct: controlled conditions + minimize dosing errors
- Mixed model on log scale with sequence, treatment, period as fixed effects and subject as random effect
- Show 90% confidence interval for ratio of geometric means lies within (0.80, 1.25) BE limits



Added value through deeper, structured thinking

Step 6. Identify assumptions for the main analysis and suitable sensitivity analyses

- Assume missing PK profiles are missing at random
- Multiple imputation with tipping point to understand the robustness of a BE conclusion

Conclusion

Regulatory guidance in BE[4,5,6,7] would benefit from requiring estimands for clarity, particularly where decisions impact drug approval or labelling:

- Bioequivalence and biosimilarity studies
- Drug-drug interaction studies (at steady state)
- Effect of food studies

Estimand framework can help us to work together better as a team to deliver better science!

Focus on you **what you want to find out (estimand)** before planning how (design and methods)

References

Please see supplementary materials at QR code.

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efpia European Federation of Pharmaceutical Industries and Associations

EFSPI European Federation of Statisticians in the Pharmaceutical Industry
Representing Statistical Associations in Europe

Does the Estimand Framework Add Value to Clinical Pharmacology Trials?

Abstract

Can the estimand framework add clarity in pharmacokinetic (PK) trials and will regulators require estimands to be stated in clinical pharmacology trials?

We apply the estimand framework of ICH E9(R1) “Addendum on estimands and sensitivity analysis”1,2 to a bioequivalence (BE) study3 and consider other PK questions of key importance to drug labelling.

PK is what the body does to the drug through the processes of absorption, distribution, metabolism, and excretion. Interest is in the profile of drug or metabolite concentrations in plasma over time summarised by the coprimary parameters: area under curve (AUC) and maximum plasma concentration (Cmax).

Generally, the goal of bioequivalence trials is to confirm the ratio of geometric means (test/reference) of AUC and Cmax with 90% confidence intervals lies within equivalence margins. Although regulators have detailed guidelines for bioequivalence and interaction trials, their scientific question(s) of interest are not clearly stated.

We explore the most common intercurrent events expected to impact the PK processes, and hence affect interpretation of the PK parameters. We also discuss the most relevant target population.

We will conclude by reflecting on existing guidelines and on how these may be adapted to incorporate the principles outlined in ICH E9(R1).

Introduction

The following steps of the ICH E9(R1) training slides[2] guided our thinking in considering BE3 of a new formulation of pirfenidone (film coated 801 mg tablet) which could replace taking three 267 mg capsules three times per day:

Step 1: Therapeutic setting and intent of treatment determining a trial objective

Step 2: Identify intercurrent events

Step 3: Discuss strategies to address intercurrent events

Step 4: Construct the estimand

Step 5: Align choices on trial design, data collection and method of estimation

Step 6: Identify assumptions for the main analysis and suitable sensitivity analyses to investigate these assumptions

Document the Estimand

Step 7 of the thinking process is “Document the estimand” is described in detail on page 3 of this supplement online, and summarised as:

In healthy adults able to tolerate 801 mg pirfenidone, the test formulation of one 801 mg film-coated tablet is compared to the reference of 3 x 267 mg capsules administered with food, by geometric mean ratio (test/reference) of pirfenidone Cmax and AUC0-∞ after a single dose, as though dosed correctly, without intake of interacting substances or unrelated intercurrent illness affecting absorption or other PK processes.

Justification of Principal Stratum Strategy

It is envisaged that only those able to tolerate 3 x 267 mg capsules of pirfenidone with food would be transitioned to the 801 mg tablet, and thus tolerability of pirfenidone is an important consideration for our principal stratum. Furthermore, differences in tolerability may be reflected in different PK properties (such as increased absorption or decreased clearance). In clinical practice, the dose of pirfenidone is up titrated to 3 x 267 mg capsules three times per day but approximately 40% of patients have tolerability issues (e.g., nausea and rash) and do not tolerate the top 801 mg dose level. The new film-coated tablet is anticipated to have similar PK profile to the three