De-risking clinical trials: forecasting and preventing disasters by pursuing an IB-derisk approach

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Introduction

Non-clinical to clinical dose translation is crucial for safety in early-phase drug trials, as disasters in past trials have shown (TGN1412 (UK, 2006); BIA-2474 (France, 2016). The main problem, is **translating complex Investigator's Brochure (IB) data into safe human trials** with proper dose range rationale (Figure 1), and EMA and (mainly) FDA guidelines are predominantly NOAEL-focused (Flap Card 1). CHDR developed the **IB-derisk: a tool to create an integrated, tabular overview of all non-clinical data** (PK, PD, Tox). The table is color-coded to severity of findings and has been implemented for years in clinical research as well as for educational- purposes (Flap Card 2).

Benefits:

- Tabular overview addresses questions prior to the clinical trial. (e.g: outliers are easily observed);
- Gives insight in the full 'dose-response curves', improving proper dose-range rationale (Flap Card 3);
- Tabular overview is in line with recommendations of the latest EMA-guideline;
- Integrate PK and PD data between different species;
- Educational tool for young researchers and regulators.

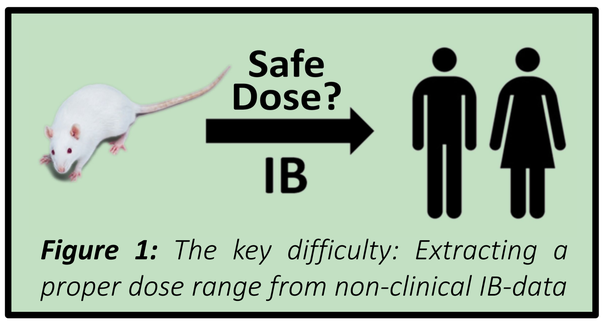

Figure 1: *The key difficulty: Extracting a proper dose range from non-clinical IB-data*

Aim

This study aims to address two key questions related to the IB-derisk approach:

1) **IB-derisk 'in foresight':** Can IB-derisk be used as a training tool and can the method aid in derisking IB's and thus improve the safety of clinical trials.

2) **IB-derisk 'in hindsight':** What is the predictive value of the IB-derisk? In other words: how accurate are its predictions based on non-clinical data, compared to the real clinical trial results from trials that have been performed.

Methods

1) **IB-derisk 'in foresight':** Students with no prior IB-review experience were trained for 1 hour on the basics of IB-derisking. They reviewed two IBs and constructed a derisk overview to solve two anonymized cases, one being a standard case (no issues) and the other BIA-2474.

2) **IB-derisk 'in hindsight':** The IB-derisk tool's predictive accuracy was assessed for 25 first-in-human CNS-active compounds by comparing anticipated dose ranges from non-clinical data with actual clinical trial outcomes.

IB-derisk 'in foresight' When Pharmacology turns Black

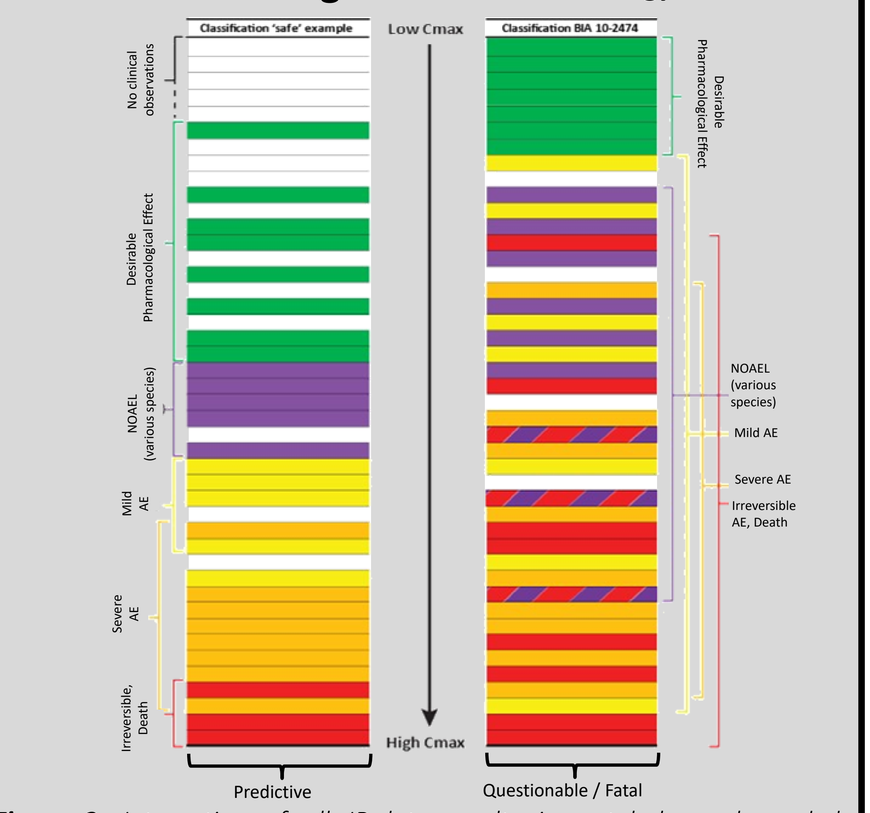

Figure 2: *Integration of all IB-data results in a tabular, color-coded overview. The table is sorted across species on relevant PK parameters like Cmax, AUC, or HED. In this way, drugs translating well from experimental animal to humans will show comparable concentration-effect relationships:*

Low Dose/AUC/Cmax ↓ High Dose/AUC/Cmax	No (pre)clinical observations (side-effects/effects)
	Desirable (Pharmacological) effects
	Mild (Tolerable) side effects
	More severe side effects (not tolerable)
	Serious irreversible side effects / death

The resulting table contains 10s or >100 color-coded rows, which shape a (hopefully) consistent picture that translates well into humans, or otherwise should enable further discussion if colors do not align (e.g. BIA-2474).
LEFT: *standard case with no issues during the clinical phase.*
RIGHT: *BIA-2474, left 1 healthy subject brain dead and 5 others at ICU.*

Results

1) **IB-derisk 'in foresight':** Students and young professionals, despite lacking IB experience, effectively used the IB-derisk approach (Figure 2) to identify safety concerns and propose dose rationale (Figure 3). For BIA-2474, 82-94% flagged major safety risks, aligning with conclusions of the formal post-mortem reports.

2) **IB-derisk 'in hindsight':** Non-clinical data predicted clinical dose ranges with 84% accuracy. Cmax predicted tolerability most closely, whereas HED was best predictor of pharmacologically active doses.

IB-derisk 'in foresight': Conclusions from Students

- *This IB fails to assess the effectivity of this drug properly.*
- *Very narrow PD-window, as no observable side effects transition into severe toxicity (incl. death)*
- *Drug results in more CNS effects during longer term dosing, and effects vary widely between species*
- *Translation to humans becomes unpredictable, particularly at high dose ranges*
- *High variability between animal species*
- *NOAEL values vary largely between species*
- *What to expect in humans? I hope it's not irreversible CNS damage…*

Figure 3: *Key student feedback (with no prior IB review experience) of the BIA-2474 case* using IB-derisk method. A summary of 10 comments can be found in Flap Card 4. Students had a Bio-pharmaceutical or Medical Sciences background (academic years 2019-2024). Comments represent 82-94% who identified major safety concerns.*
** The BIAL-trial (Rennes, France 2016), left 1 healthy volunteer brain dead and 5 others at the ICU.*

IB-derisk 'in hindsight' IB-derisk predictability: overlap preclinical vs clinical data

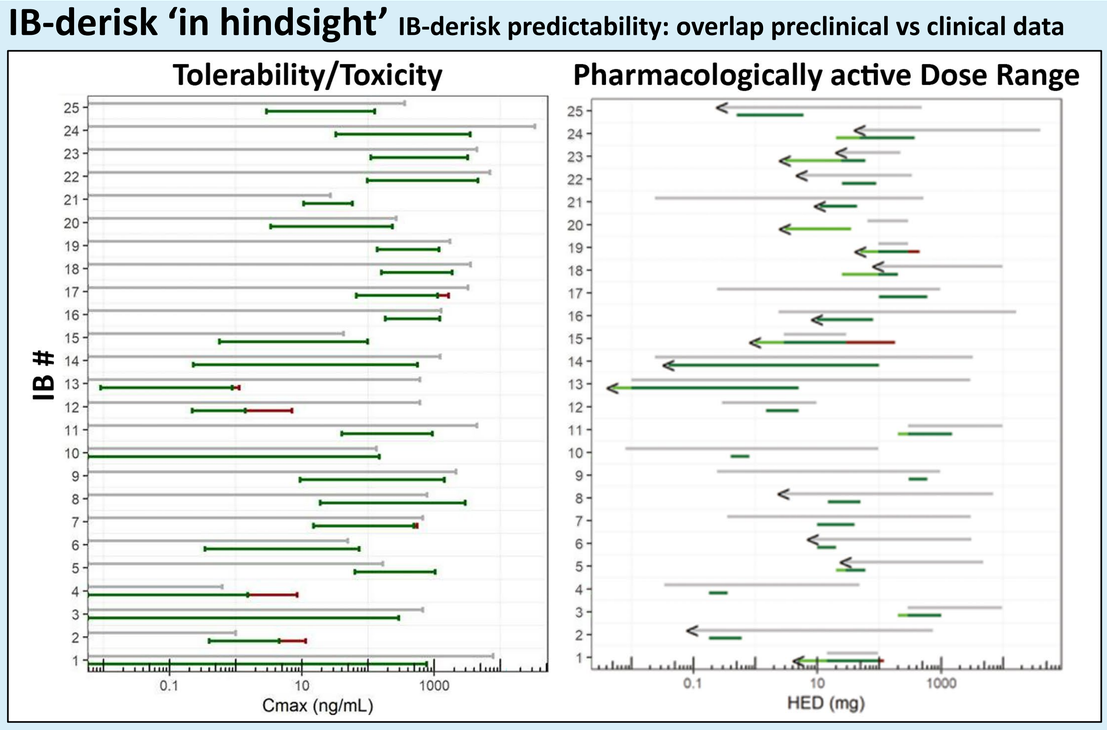

Figure 4: *Overlap Ranges for both preclinical and clinical data regarding using the IB-derisk approach:*
LEFT: *Safety/tolerability. Tolerability was best predicted by Cmax with only 32% of clinical studies reporting well-tolerated doses above the NOAEL value and only 16% of clinical studies reporting unacceptable side effects at values below the NOAEL.*
RIGHT: *Pharmacologically active dose ranges. The best predictor was HED, with 84% overlap between preclinical and clinical dose ranges.*

Conclusions

The IB-derisk approach provides an integrated tabular overview that:

- Aids in **meaningful integration** of preclinical to clinical data;
- gives rise to **relevant questions** about drug-translatability;
- **facilitates communication** amongst researchers and regulators;
- serves as **teaching tool** for future professionals in drug development.

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