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SCIENCE MEDICINES HEALTH

BOS1 Regulatory Discussant

Walter Janssens, Federal Agency for Medicines and Health Products, Belgium

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First in Human Doses

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Outline:

Use of M&S in FIH studies.

Dose Escalation

Gaps

Microdose Clinical Trials

2. Use of M&S in FIH studies.

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Starting dose based on NOAEL: rarely used alone

Starting dose based on NOAEL and expected active dose:

– Used when target is not expressed in mammalians, e.g. anti-infectives

– Used when target is well known

Starting dose based on Minimal Anticipated Biological Effect Level:

- Used when target is unknown
- Used with first in class substance

– Used when a cascade of events could be triggered

– Used when dose response curve is steep

– How reliable is the model?

3. Use of M&S in FIH studies.

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Uncertainty factors:

- Should be highlighted
- High risk as defined in the guideline on mitigation of risks in FIH trials
- Unexpectedly high exposure in humans
- Unexpected human specific metabolites, that are unexpectedly active on target or otherwise
- Unexpected high activity or activity in humans not predicted from animal models
- The unexpected cannot be modelled

Safety margins:

- Should be realistic
- Intended to prevent high activity at first human exposure
- Not intended to cover insufficient data
- Not to be used “cumulatively”

4. Dose Escalation

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Choice of a safe (inactive?) starting dose is important, but:

Observations in humans at low doses should not create a sense of safety with increasing doses

Pharmacological and toxicological effect will occur or be more prominent at higher (active?) doses:

- Use M&S to guide dose increments
- Use M&S to establish maximal allowed dose
- Include observations at lower doses in humans to refine models

5. Gaps

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M&S is used by most companies submitting FIH trials

There are models which are frequently used: can these be considered validated?

Is there a need for further validation of models for general use?

How can models developed for a particular purpose best be justified?

6. Microdose Clinical Trials

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Exploratory clinical trials are now recognised in ICH M3

Usually these trials are conducted to decide on the progression into further development or to make a choice between drug candidates

These trials, at low exposure, could also be helpful to obtain necessary information in humans to refine M&S

Stopping rules and definition of maximal allowed exposure are very important for these trials

In particular microdose trials might be useful to obtain data on PK and interaction with the target that could be used for refinement of the model