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AI in generic drug development - experience and opportunities

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Generic industry focus

Bioequivalence:

- approval of **ANDA**
- **postapproval changes**

To predict BE outcome focus on **differences between test and reference** formulations is needed.

Required properties of modeling tools for BE predictions

- Flexibility - combination of text and numerical features.
- Inclusion of all available BE studies in a model.
- To enable modeler to include knowledge into a system.
- Transparency.
- Capability to model complex nonlinear systems and to process vague, ambiguous, imprecise, noisy input information.
- PE < 10% for T/R ratio of PK parameters, to meet BE limits.

AI models can meet the requirements

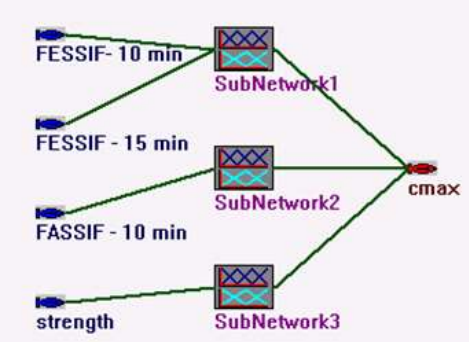
Neuro-fuzzy models:

Fuzzy logic
(descriptive presentation)

&

Neural networks
(structure and learning rules)

Fuzzy rules: *IF x=A THEN y=B*



Model in Neuframe version 4.0, Neusciences 2000

AI models for IVIVR in generic industry

INPUTS

Combinations of :

dissolution data in different media, composition (numeric or text variable), particle size, fed/fasting conditions (text variable), solubility , formulation strength, technology type...

IVIVR

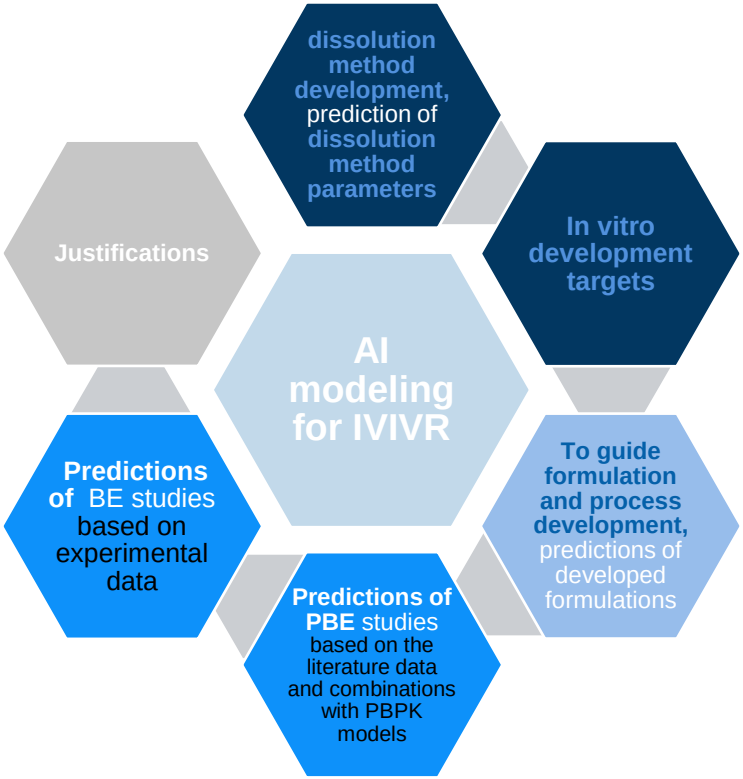
built on **known input and output** data of more PBE/BE studies

OUTPUTS

Cmax T/R ratio

AUC T/R ratio

The role of AI modeling in a generic drug development



AI modeling IVIVR experience – prediction performance

External PE% **Cmax** ratio

Median: 5.8%

External PE% **AUC** ratio

Median: 3.6%

External PE% **Cmax** ratio

Mean: 7.5%

N of models: 163

External PE% **AUC** ratio

Mean: 4.6%

N of models: 115

PE% target for BE predictions:

≤ 10% for Cmax or AUC ratio

Limitations of AI models

- Limited transparency - model knowledge is not in the form of a mathematical equation.
- Overfitting - limited databases.
- A reliable database is crucial for the quality of the empirical model.
- Lack of guidelines to support AI models.
- Trust in AI models is currently limited.

Suggestions for regulatory opportunities of AI models in generic drug development

- AI models could serve as level A or multiple level C correlations (for IR and MR formulations).
- Specifications setting.
- Safe space predictions.
- Biowaivers of lower strengths, postapproval changes.
- Justifications for new dissolution methods.
- Increase of knowledge and faster development based on processing big data – QbD support.

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- IVIVC group
- Pharmaceutical Development
- Clinical Development

References

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Thank you

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