The role of modeling and simulation in the approval of generic drug products

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Pharmacometrics and Regulation

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Brazilian Regulatory Structure

- ✓ Positive Law
- ✓Resolutions, Normative Instructions and Guides
- ✓Generality versus Detailing
- ✓**Pharmacometrics: no specific requirement**

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Efficacy and Safety Analysis Guideline for Drug Registration Assessment

- ✓Transparency of work processes and dialogue with the regulated sector
- ✓Proposed by Anvisa experts in drug registration department (GESEF)
- ✓References: international regulatory agencies and ICH Guides

Do pharmacokinetic data allow characterizing the absorption profile, distribution, metabolism and excretion of the drug?

- Identify whether data were obtained from specific clinical studies, data obtained from modeling (M&S), population pharmacokinetics or clinical pharmacology studies conducted with other pharmaceutical forms, routes of administration or other doses

Is there an influence of intrinsic factors on the pharmacokinetics of the drug?

Identify whether the data were obtained from specific clinical studies, subgroup analysis data, data obtained from modeling (M&S) or population pharmacokinetics.

Is there an influence of extrinsic factors on the pharmacokinetics of the drug?

- Identify whether the data were obtained from specific clinical studies, subgroup analysis data, data obtained from modeling (M&S) or population pharmacokinetics.

- Present data from clinically relevant pharmacokinetic interactions with other medicines or substances.

Are there data from population pharmacokinetic studies?

- Present data related to inter- and intra-individual variability that may be due to intrinsic and extrinsic factors obtained through population pharmacokinetic studies.

Population Pharmacokinetics

- Study of the sources of variability of drug concentrations in the target population that received clinically relevant doses of the drug under study.

- It seeks to identify the measurable pathophysiological factors that alter the dose/response ratio and the extent of these changes so that the doses of the drug can be changed appropriately if such changes are associated with clinically significant changes in the therapeutic index.

Are the pharmacological characteristics of the medicine adequately described in the proposed package leaflet texts?

- If the pharmacokinetic properties described in a package leaflet were obtained from other routes of administration, other pharmaceutical forms, other doses, data obtained from modeling (M&S) or population pharmacokinetics, this information should be described in the package.

Challenges and Trends

Regulatory Convergence

- ✓**2019: Anvisa was accepted as part of the ICH Management Committee**

- ✓Guides with Anvisa participation that have interface with pharmacometrics:
  - E11A: Paediatric extrapolation
  - M12: Drug Interaction Studies

- ✓New Topic: Model-Informed Drug Product Development

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Seminar Anvisa +10

- ✓ **Develop and stimulate the use of data modeling, simulation and extrapolation techniques:** these techniques can support the efficiency of new drug products develpment, since they can reduce the need or optimize the design of clinical studies.

Anvisa's Experience on PBPK/PBBM

- ✓ **Clinical Relevant Drug Products Specifications;**
  - Dissolution specifications;
  - Bridging between biorelevant and quality control (QC) dissolution methods;

- ✓ **Bioequivalence and PK comparability;**
  - ✓ **Food Effect**
  - ✓ **Biowaiver**

- ✓ **Post-approval CMC changes or manufacturing site transfer**

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Challenges

- ✓ Training;
- ✓ Harmonization of Terms, Protocols and Reports;
- ✓ Integration and Engagement Anvisa/University/Industry.

Obrigado!

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