2015 Science Writers Symposium

Modeling and Simulation in Regulatory Review: A CDER Perspective

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Supporting CDER's Mission

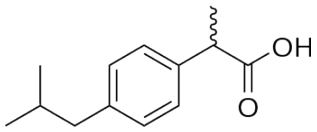
CDER's mission: Protect and promote public health by helping to ensure that human drugs are safe and effective for their intended use, that they meet established quality standards, and that they are available to patients.

Modeling and simulation supports this mission and is aligned with FDA's strategic priorities

- Modernize toxicology
- Stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes
- Ensure FDA readiness to evaluate innovative emerging technologies
- Harness diverse data through information sciences to improve health outcomes

Modeling and Simulation at CDER

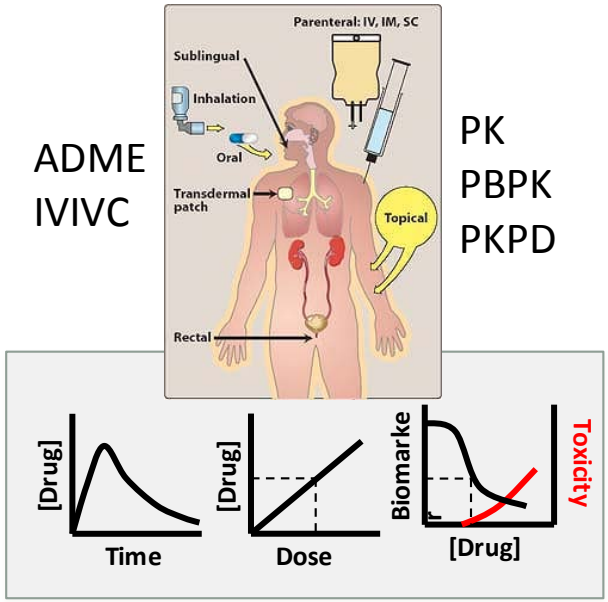
CHEMISTRY MODELS



Docking models
(Q)SAR
Formulation
Manufacturing

EXPOSURE MODELS

ADME
IVIVC



PK
PBPK
PKPD

BIOLOGY MODELS

Disease
Pharmacology
Toxicology

Gene
Proteins
Pathways
Cells
Organs
Patients
Populations

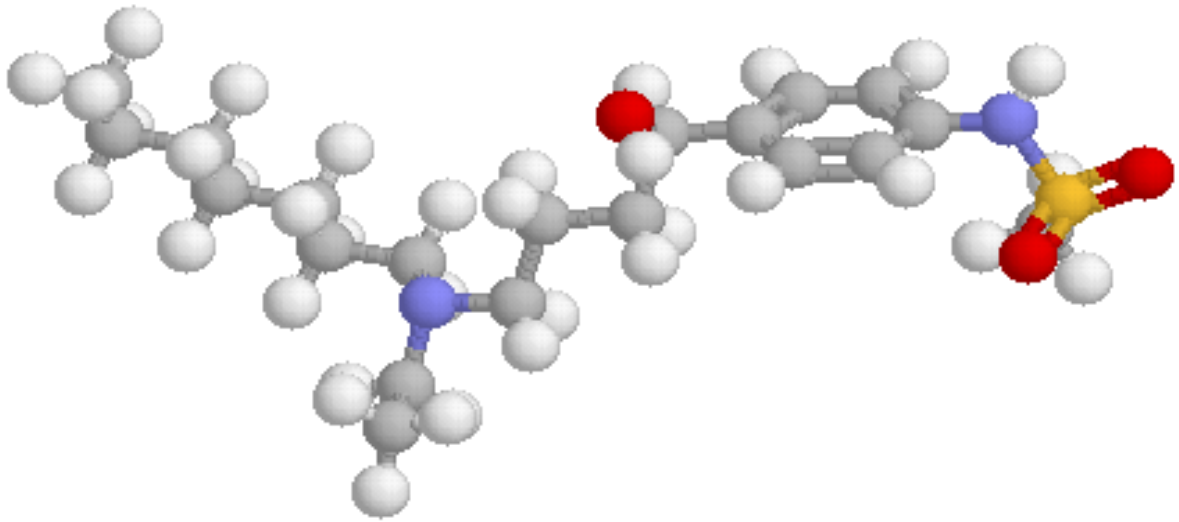
STATISTICAL MODELS

e.g., Clinical trial design Benefit-risk analysis Model validation

(Q)SAR Modeling

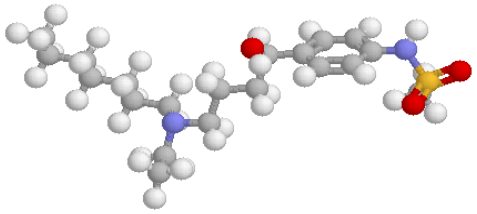
- Investment in regulatory research led to development of a model that is used by CDER to support regulatory review decisions
- (Q)SAR = (Quantitative) Structure-Activity Relationship

➔ Predicts toxicity from chemical structure



Predicting Toxicity from Chemical Structure

- Scenarios arise during drug development where toxicity of a chemical is unknown.
- Conventional practice is to make the chemical and then test it in toxicology studies.
  - Time-consuming
  - Expensive
  - Impractical
- Predicting toxicity directly from a chemical structure is very powerful.
  - Perform virtual screens of new drug candidates.
  - Assist in the interpretation of toxicology findings.
  - Assess the safety of drug impurities.



(Q)SAR Modeling: How Does It Work?

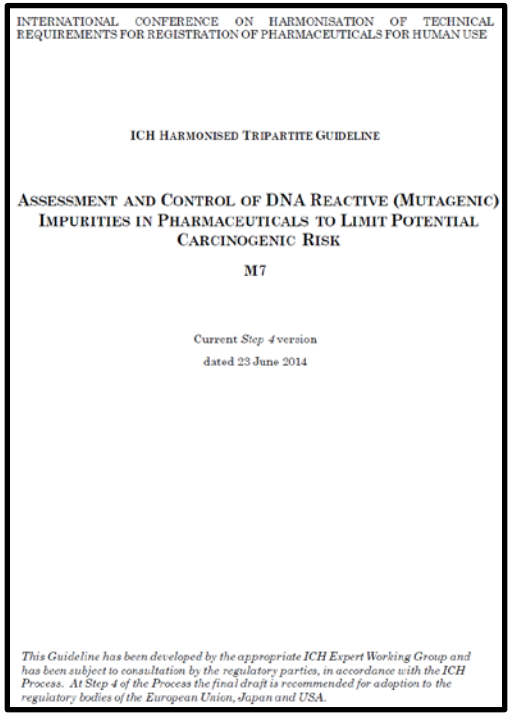
- (Q)SAR = (Quantitative) Structure-Activity Relationship
  - Modeling identifies associations between attributes of chemical structures and biological activity (toxicity)
  - General assumption: Similar molecules exhibit similar chemical and biological properties
  - Toxicity can be explained by chemical structure
- Model learns from the results of actual laboratory testing
  - Use a computer to evaluate "pieces" of chemical structures to find those associated with toxicity ➔ structural alerts
- Model can be used to make a prediction of a new chemical's toxicity based on its structure
  - Rapidly
  - Consistently

Early Regulatory Research Efforts

- (Q)SAR modeling research began at CDER in late 90s.
  - Developed in-house databases
  - Modeling software obtained through collaboration agreements
  - Models published in peer-reviewed journals
- Efforts expanded to include other software platforms and endpoints, starting in early 2000s.
  - Emphasis on transparency and interpretability
  - Rigorous validation
  - Used at CDER for informational/decision support purposes

Evolution of (Q)SAR Towards Regulatory Acceptance

- (Q)SAR for safety assessment of drug impurities considered by CDER in 2007
  - Draft CDER Guidance in 2008
  - Internal collaboration with CDER reviewers to ensure utility of models
- ICH M7 finalized in June 2014
  - "Fit-for-purpose"
  - (Q)SAR predictions accepted by FDA/CDER in place of conventional testing for drug impurities



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

M7

Current *Step 4* version

dated 23 June 2014

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Application of ICH M7

- Scale-up of drug synthesis from bench-top level to production level for large clinical trial results in a previously untested impurity
  - Does the impurity pose a mutagenic risk?
    - —Synthesis of impurity and testing could take 3–4 months
- Impurity structure run against two (Q)SAR models in accordance with ICH M7
  - Negative predictions indicate lack of mutagenic concern
  - No further testing is required

Importance of Regulatory Research

- Inclusion of (Q)SAR in ICH M7 would not have been achieved without a rigorous regulatory research program at FDA/CDER.
- It has enabled us to:
  - Identify appropriate use cases for (Q)SAR models in a regulatory setting;
  - Provide a science-based rationale for how (Q)SAR models should be used; and
  - Support FDA's position in external interactions.

Regulatory research in modeling and simulation is critical to advancing the state-of-the-science.

The Chemical Informatics Program Team

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