Using Cheminformatics to Support Drug Safety Assessment

Naomi L. Kruhlak, Ph.D.
Division of Applied Regulatory Science
Office of Clinical Pharmacology
Office of Translational Sciences
FDA’s Center for Drug Evaluation and Research
Naomi.Kruhlak@fda.hhs.gov

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Outline

- Introduction to chemical informatics
  - Structure-based searching
  - (Q)SAR modeling

- FDA/CDER technical capabilities and use cases
  - Regulatory research
  - (Q)SAR model and database application

- Safety assessment of drug impurities
  - ICH M7 guideline and (Q)SAR
  - Expert review of (Q)SAR predictions

- Emerging technologies
Introduction to Chemical Informatics
Chemical Informatics

- Interface between chemistry, computational science, and information management techniques, including:
  - mining, organization, and analysis of chemical information
  - development of databases and predictive models

- At CDER, chemical informatics interfaces with biology—specifically, pharmacology and toxicology—where the central component is chemical structure.

- Put simply, we develop and apply tools and methods for:
  - Data look-up
  - Analog searching
  - Predicting biological activity

=> ...using chemical structure
Supporting Regulatory Decisions

- Has FDA/CDER seen this chemical before?
- Are experimental data available?
- Are there data for structurally related compounds?
- Can we predict its toxicity?
- Have we previously performed a (Q)SAR analysis?
- Is the Applicant’s (Q)SAR analysis acceptable?
Chemical Structure-Based Searching

- Search a database using a chemical structure
  - Exact structural match
  - Sub-structural search
  - Whole molecule similarity

Exact match
- Data lookup for single molecular entity
- Unambiguous way to identify a compound
- Returns data across all toxicological endpoints

Ibutilide
Sub-Structure Searching

- Returns multiple hits containing a particular sub-structure, e.g., an epoxide
  - Typically paired with an endpoint of interest (e.g., bacterial mutagenicity)

![Diagram of sub-structures with 399 and 16 hits]

- Can use the data from the analogous structures to predict the activity of the query substructure (“read-across”)
Data for structural analogs allows manual structure-activity relationship (SAR) analysis, or “read-across”
(Q)SAR Modeling

- (Q)SAR = (Quantitative) Structure-Activity Relationship
  - Modeling identifies associations between attributes of chemical structures and biological activity (e.g., 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 or clinical experience
  - Use a computer to examine “pieces” of chemical structures to find those associated with activity
    - structural alerts
  - Can also identify attributes that mitigate activity

- Model can be used to make a prediction of a new chemical’s toxicity based on its structure
  - Fill data gaps when empirical data are unavailable or inadequate
  - Prioritize testing of new compounds
Chemical Informatics at FDA/CDER
FDA’s Predictive Toxicology Roadmap

• Developed by FDA’s Toxicology Working Group
• Published December 2017

“...a comprehensive strategy is needed to evaluate new methodologies and technologies for their potential to expand FDA’s toxicology predictive capabilities and to potentially reduce the use of animal testing.”

Promising technologies in predictive toxicology:
1. Microphysiological systems like tissues or organs on a chip
2. Alternative test methods for reproductive toxicity testing
3. **Computational toxicology**
   - FDA’s research programs contribute to updating existing and developing new quantitative structure-activity relationship (QSAR) programs and to devising new computational approaches.
4. In vitro alternatives
5. Quantitative risk assessment (QRA) addressing the complex chemical mixtures of tobacco products
6. **Read-across methodology**

Chemical Informatics at FDA/CDER

- Applied regulatory research supporting drug safety:
  - Create chemical structure-linked toxicological and clinical effect databases
  - Develop and enhance toxicological and clinical effect prediction models through external collaborations
  - Develop best practices for the application of computational models

- Computational Toxicology Consultation Service
  - Provide (Q)SAR evaluations for drugs, metabolites, impurities, degradants, etc. to FDA/CDER safety and quality reviewers
  - Perform structure-based searching for read-across purposes
  - Provide expert interpretation of (Q)SAR data submitted to FDA/CDER
  - Maintains a repository of chemical structures evaluated internally or used for CDER cheminformatics projects (currently ~30K)
Clinical AE Endpoints:
- Liver toxicity
- Cardiotoxicity
- Renal toxicity

Non-Clinical Toxicology Endpoints:
- Genetic toxicity
- Rodent carcinogenicity
- Reproductive/developmental toxicity
- Phospholipidosis

Pharmacological Effects:
- Opioid receptor activity
- Blood-brain barrier permeability

FDA/CDER Current Capabilities

Chemical Registration System

Web-based Searchable Databases

In-House (Q)SAR Consult Database

Chemical Structures

Predictive Models

Data Sets

Consultations

Training Sets:
Non-Clinical Toxicity
Clinical AEs

Benchmarking

Reference datasets:
Validation
Read-across
(Q)SAR Use Cases at FDA/CDER

- **Non-clinical review**
  - ICH M7 compliant mutagenicity (Q)SAR assessments:
    - Synthetic intermediates, starting materials, reagents, and degradants that may be present in finished drug product
    - (Q)SAR may be used to evaluate an impurity up to 1mg for mutagenic potential in place of an in vitro assay
  - Interpretation of equivocal or inadequate study results from non-clinical studies (e.g., genetic toxicity, carcinogenicity)

- **Clinical/Post-market safety review**
  - Investigation of a weakly positive adverse event signal (e.g., hepatotoxicity)
  - Hypothesis generation, interrogation of possible structural moiety responsible
  - Identification of similar drugs with known toxicity profiles

Safety Assessment of Drug Impurities
Drug Impurities

- Why are we concerned with impurities?
  - Unlike API, impurities offer no direct benefit to the patient
  - Impurities will be present regardless of the control strategies applied
  - By their nature, some impurities are reactive and may possess mutagenic potential
  - Mutagenicity is tied to the multi-step process of carcinogenicity
    - Effects will not be evident in patients for many years
    - Not identified through clinical monitoring
Striking a Balance

- Evaluating the mutagenic potential of drug impurities is an important component of safety assessment

- From a practical standpoint:
  - A cautious approach is warranted but conducting an empirical assay for every potential and known impurity is not feasible or justified

  ➔ Impurity evaluation process must balance the need for high-throughput with the regulatory imperative of maximizing patient safety
(Q)SAR for Impurities

- (Q)SAR provide the high-throughput process needed to handle a large volume of impurities
- Demonstrated to have adequate sensitivity for predicting bacterial mutagenicity (~85% depending on systems used, test sets evaluated, etc.)
  - Critical for patient safety
- For impurities:
  - Considered “fit for purpose”
  - Recommended by regulatory agencies
  - State-of-the-art approach for assessing mutagenicity
Goal of hazard assessment is to assign impurity class based on experimental data or (Q)SAR.

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Known mutagen</td>
</tr>
<tr>
<td>2</td>
<td>Known mutagen-unknown cause (bacterial or rodent carcinogen)</td>
</tr>
<tr>
<td>3</td>
<td>Alerting structure of the no mutagenic</td>
</tr>
<tr>
<td>4</td>
<td>Alerting structure of a substance or drug intermediate and are non-mutagenic</td>
</tr>
<tr>
<td>5</td>
<td>No structural alerts with sufficient evidence of mutagenic</td>
</tr>
</tbody>
</table>

- Mutagenic
- Non-mutagenic

experimental data
(Q)SAR
experimental data or (Q)SAR
Application of Expert Knowledge

**Model output** “... can be reviewed with the use of expert knowledge in order to provide additional supportive evidence on relevance of any positive, negative, conflicting or inconclusive prediction and provide a rationale to support the final conclusion.”

- Identify and interpret alerting portion of the molecule
- Assess training set structures used to derive an alert and mitigating features
- Consider mechanism of reactivity, where possible
- Consider data from structurally similar compounds (analogs) not used by the model

**Expert knowledge is applied to all (Q)SAR analyses conducted in-house by FDA/CDER**
CDER Computational Toxicology Consultation Service

(Q)SAR Consults, 2009-2018

- Average of 17 chemicals evaluated per week
- Web-based (Q)SAR consultation submission system
- Turnaround time of 10 business days

ICH M7 Finalized
880 chemicals
297 consults
Other Chemical Structure-Based Modeling

- **Molecular docking**
  - **WHAT:** Uses an x-ray crystal structure of a receptor to simulate binding of a ligand in 3D by generating energetically favorable poses
  - **WHY:** Predicts the binding potency of uncharacterized substances (e.g., opioids) to assess their abuse potential and public health risk

- **Pharmacological receptor binding prediction**
  - **WHAT:** Predicts biological receptor binding profiles based on structural similarity to known binders
  - **WHY:** Identifies potential off-target binding and subsequent adverse effects (e.g., DILI, CNS toxicity) of a drug in the absence of clinical data

Emergency Assessment of Drugs of Abuse

**Public Health Assessment via Structural Evaluation, or PHASE**

- Evaluate the risk a newly-identified drug of abuse poses to public safety using chemical structure
- Method developed in response to the influx of modified fentanyl on the street market
- Developed as part of a multi-component approach that includes structural similarity assessment, biological target prediction, and molecular docking at mu opioid receptor
- Supports scheduling recommendations for new substances

Concluding Remarks

- Chemical informatics is a key component of drug safety review at CDER
- The use of structure-based searching and (Q)SAR models is recommended in regulatory guidance:
  - Mutagenicity (Q)SAR models are deemed “fit for purpose” for impurities under ICH M7
  - Models for other endpoints or new chemical structure-based methodologies are used for decision-support or investigational purposes
- Ongoing need to update databases and models
  - Underscores the importance of identifying model strengths and weaknesses, and tracking chemicals that have already been evaluated
  - Consultation requests inform modeling direction
  - Collaborative mechanisms facilitate access to updated modeling tools and supplemental databases
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