Introduction into PharmaPendium

Informed decision making throughout Pharmaceutical development

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We suggest viewing the presentation in full screen.
Submit your questions

Ask a question

Type your question here...
Today’s agenda

1. **Background into PharmaPendium**: making informed decision during Pharmaceutical development
2. **Full text searching**: Retrieving regulatory insights from hard-to-access regulatory documents
3. **Retrieving safety data**: Accessing high quality safety data extracted from literature and regulatory documents
4. **Analyzing FDA post-market data**: Analyzing post-market adverse event to inform decision making
5. **Q&A**
1) PharmaPendium Background

Making informed decisions during Pharmaceutical development
The PharmaPendium value proposition

Costs to bring a new drug to the market: $2.6B

Time needed to develop a new drug: 12 yrs

Clinical success rate is low: 9%

PharmaPendium®

1. Help fail drugs faster
2. Optimize clinical success
Pharmaceutical development: High Pain, high gain

Take up to 15 years, high costs, high risk, no revenue,

1. Improve success rate, reduce risk (fail early)
2. Reduce development time
3. Work cost effective
4. Work innovatively

High gain, patent protection, highly regulated

1. Stay on the market as long as possible
2. Be compliant
3. Work cost effective
PharmaPendium: the main use case

1. Filing for approval: regulatory authorities compare safety, effectiveness and deliverability with drugs already on the market (Risk/benefit analysis)

2.Drug are only approved if they outperform drugs already on the market

3. Therefore, during development and approval you need to be fully informed on regulatory data on drugs that are already on the market!!
Our Process and Industry's challenge –

making regulatory documents accessible

**Inputs**
- FDA Drug Approval Documents back to 1938
- EMA Drug Approval Documents back to 1995
- FDA AERS
- FDA Advisory Committee Meeting Reports
- Journal Articles

**Transformation**
- Make documents text searchable
- Define taxonomy
- Develop databases structure
- Manual review by panel of experts
- Extract observations on Safety, Pharmacokinetics, Efficacy and Metabolizing enzymes and Transporters

**Outputs**
- Searchable, indexed database all linked back to original documents
- All extracted information searchable across drug, class and chemical structure
- Data ready to be exported into analytical modeling tools
Accessing critical information for the most comprehensive safety risk assessment

Unstructured, poorly searchable data

Structured, high quality regulatory data that can be easily retrieved from the entire approval package
Searchable FDA/EMA Drug Approval Docs, extracted data, expert taxonomies and prediction tools

**Text searchable Content**
- FDA approval packages (1938 – now)
- EMA approval packages (1995 – now)
- FDA Advisory Committee Meetings
- DESI (Drug Efficacy Study Implement’n)
- Meyler’s, Mosby’s
- FAERS (FDA Adverse Event Reporting System)

**Taxonomies & Search strategies**
- Drugs/Drug Classes
- Targets/Target Classes
- MedDRA (Adverse Events)
- Indications
- Chemical Structures/Substructure
- Species
- Concomitants
- Endpoints
- .....and more!

**Preclinical AND Clinical**
- Drug Safety data
- Pharmacokinetic data
- Met. Enzymes and Transporters data
- Efficacy data
- Activity data

**Prediction Tools**
- DDI Risk Calculator

**Summary Table and Visualization Analysis**
PharmaPendium key differentiators

Unique content

High quality data

Expert taxonomies

Easy retrieval

Unprecedented access to preclinical and clinical information to make informed drug development decisions
How can PharmaPendium be used?

Example User Questions:

- Can I find safety, efficacy and DMPK data to support my analysis of in vitro and in vivo test results?
- Can I compare my drug to approved drugs to help optimize my drug safety analyses and trial design?
- How can I assess PK parameters and potential drug-drug interaction risks for my drug candidate?
- What support can I get for making my case to the regulatory authorities?
- What are the efficacy benchmarks that must be met to compete?
- Which primary endpoints were used during Phase III clinical trials for similar drugs?
- Can I cite a previously-run experiment from a similar drug?

Possible use cases:

- Prioritize drug candidates
- Assess small and large molecule drug safety
- Anticipate and mitigate risk
- Answer which drug candidate to progress
2) **Full text searching**

Retrieving regulatory insights through hard to access regulatory documents
Example question #1

For my drug under development, I would need to test for anti-drug antibodies.

*What immunoassays have other companies used to detect anti-drug antibodies, for drug currently on the market?*

Impact: getting it right immediately, de-risk development
Setting up a quick search

Type: “anti-drug antibody” AND immunoassay
### Results

**PharmaPendium**

**Search res...** Jump to: page 1

159 records from Documents: ["anti-drug antibody" AND immunoassay with synonyms]

<table>
<thead>
<tr>
<th>ID</th>
<th>Document with context</th>
<th>Drug name</th>
<th>Source</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>N/A</td>
<td>FDA Advisory Committee Documents</td>
<td>2016</td>
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<td>2</td>
<td>Pharmacology Review 761091/S-000 Part 02 PDF 1085k</td>
<td>Trastuzumab</td>
<td>FDA approval packages</td>
<td>2017</td>
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<td>4</td>
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<td>Bezafibrate</td>
<td>FDA approval packages</td>
<td>2016</td>
</tr>
</tbody>
</table>

**FDA approval package document: Review 125294/S-000 Part 06 PDF 963k**
Results

There was a problem

The Sponsor has not validated a sensitive and specific screening assay for the evaluation of binding antibodies against XM02. Recalculation of the cut point value for the direct ELISA assay did not include a statistically significant sample number for the indicated patient populations, namely breast cancer, lung cancer and non-Hodgkin lymphoma. Therefore, the estimated percentage of patients positive for binding antibodies against the product is questionable. Similarly the Sponsor does not have adequate confirmatory and neutralizing assays.

The safety database for XM02 does not indicate that there were patients who lost efficacy or developed neutropenia during the course of the trial. Furthermore, preliminary immunogenicity data from the inadequate assays indicates a low immunogenicity rate, ~2.4%. The original assays would have detected robust anti-drug antibody responses, but it were not validated for the detection of low anti-drug antibody responses. Since the risk to safety and efficacy are low we find that it is acceptable to allow Teva to correct their

And a solution

biotinylated Tbo-filgrastim as capture agent immobilized onto the streptavidin coated plate, and ruthenylated Tbo-filgrastim as detection agent. When anti- Tbo-filgrastim antibodies are present, an immune complex can be formed in the assay, which then can be detected by light emission. Alternatively, a homogeneous bridging ELISA will be developed for screening of anti- Tbo-filgrastim antibody responses. The method will be based on the formation of sandwich immune complex of anti- Tbo-filgrastim antibody with biotinylated Tbo-filgrastim and digoxigenin (DIG)- conjugated Tbo-filgrastim in solution phase. The complex then can be detected in an avidin-coated plate with labeled anti-DIG antibody. The assay development and validation will be conducted by following FDA draft Guidance for Industry - Assay Development for Immunogenicity Testing of Therapeutic Proteins (December 2009) and the Mire Sluis et al. white paper. The assay parameters will include sensitivity, precision, accuracy, interference and minimal required sample dilution, drug tolerance, specificity, robustness and sample stability.

- Date of submission of the validation protocol will be August 15th 2012
- Final report submission date will be December 15th 2012

Comment to the file:
In response to our request the Sponsor commits to providing validation protocol and final report by specific dates. This is acceptable for reasons noted above.

going it right immediately, de-risk development
3) Retrieving safety data

Accessing high quality safety data extracted from literature and regulatory documents
Example question #2

I am developing a new drug acting on Cyclin-dependent kinase.

What effects on QT prolongation have been observed in drugs that act on that same target?

• Impact: Regulatory insights, competitive intelligence/positioning, animal model selection and benchmark
Safety pharmacology – QT prolongation studies

QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

Since 2005, the FDA and EMA have required that nearly all new molecular entities be evaluated in a Thorough QT (TQT) study to determine a drug’s effect on the QT interval.
Multiple entry points to start a drug safety search

PharmaPendium®

Browse

Drug safety module

Drug safety module

FDA adverse event data system
Browsing for drug safety data by targets

Select

Type and “enter”

Select
The primary target–drug association table

<table>
<thead>
<tr>
<th>Drugs where target is primary</th>
<th>Sources where Primary Target – Drug association is found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FDA</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>FDA</td>
</tr>
<tr>
<td>Ribociclib Succinate</td>
<td>FDA</td>
</tr>
</tbody>
</table>

- Informs where a certain primary target – drug association is extracted from
- Access to extracted data

Biology data:
- View Pharmacokinetic Data
- View Metabolizing Enz. & Trans. Data
- View Drug Safety Data
- View FAERS Data
- View Efficacy Data
## Translational insights

<table>
<thead>
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<th>Condition</th>
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<th>No Data</th>
<th>Count</th>
</tr>
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<tbody>
<tr>
<td>Administration site reactions</td>
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<td>no data</td>
<td>43</td>
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<tr>
<td>Body temperature conditions</td>
<td>1</td>
<td>27</td>
<td>811</td>
</tr>
<tr>
<td>Complications associated with device</td>
<td>no data</td>
<td>no data</td>
<td>4</td>
</tr>
<tr>
<td>Fatal outcomes</td>
<td>19</td>
<td>23</td>
<td>2454</td>
</tr>
<tr>
<td>General system disorders NEC</td>
<td>30</td>
<td>132</td>
<td>12389</td>
</tr>
<tr>
<td>Acquired gene mutations and other alterations</td>
<td>no data</td>
<td>no data</td>
<td>2</td>
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<tr>
<td>Adverse effect absent</td>
<td>no data</td>
<td>no data</td>
<td>41</td>
</tr>
<tr>
<td>Asthenic conditions</td>
<td>12</td>
<td>102</td>
<td>8848</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1</td>
<td>26</td>
<td>1609</td>
</tr>
<tr>
<td>Decreased activity</td>
<td>11</td>
<td>no data</td>
<td>11</td>
</tr>
<tr>
<td>Fatigue</td>
<td>no data</td>
<td>76</td>
<td>7106</td>
</tr>
<tr>
<td>Malaise</td>
<td>no data</td>
<td>no data</td>
<td>1479</td>
</tr>
<tr>
<td>Sluggishness</td>
<td>no data</td>
<td>no data</td>
<td>12</td>
</tr>
<tr>
<td>Feelings and sensations NEC</td>
<td>no data</td>
<td>no data</td>
<td>1081</td>
</tr>
<tr>
<td>Gait disturbances</td>
<td>no data</td>
<td>no data</td>
<td>437</td>
</tr>
<tr>
<td>General signs and symptoms NEC</td>
<td>4</td>
<td>11</td>
<td>1140</td>
</tr>
</tbody>
</table>
Multiple search limits

**PharmaPendium**

Browse ▼ Search ▼ My tools ▼ ▼

New

Safety data search
Preclinical, clinical and post-market data

**Drugs**
- Add drugs by drug class or drug name
- Add drugs by primary target or primary target class
- Add drugs by indication

**Adverse Effects / Toxicity**
- Add Adverse Effects / Toxicity

**Species**
- Add species

**Sources**
- Add sources
We extract drug safety data from:

Dating back to 1938*
Dating back to 1995

Selected literature sources

- New extracted data is added to PharmaPendium monthly
- Content updates can be found [here](#)

*Requires FDA classic collection. Regular FDA coverage start 1992
Add drugs based on primary targets

1. All drug/target associations are from xPharm®, Mosby's Drug Consult™, FDA Approval Package, EMA EPAR documents.
2. Targets are indexed using PharmaPendium’s dedicated target taxonomy

1) Type “Cyclin-dependent”

2) Select

3) Select
Add adverse effects

1. PharmaPendium uses MedDRA taxonomy for both preclinical, clinical and post-market data
2. Delivers insights on how well a preclinical effect translates into the clinic

1) Type “QT” and hit enter
2) Select
3) Select

Done
Select species

1) Type “dog”

2) Select

3) Select

Add species

Done
Search over 3 dimensions

search with PharmaPendium’s target, adverse effect and species taxonomy
Dose-dependent QTc-interval prolongation was noted in dogs at ribociclib doses ≥20 mg/kg when compared to pretest values. The amplitude of the QTc prolongation and the number of time-points noted with QTc prolongation increased with increasing dose levels, whereas the time of onset was similar at all dose levels. Mean increases of QTc at 20, 50, and 100 mg/kg versus vehicle control, for the time period of 1.75 hours postdose until the end of the recording period, were 12.1 ms (+5.3%), 23.4 ms (+10.2%), and 37.9 ms (+16.5%), respectively. Individual changes in QTc-interval postdose versus pretest values correlated well with both C_max and AUC_{0-48h}. The group mean exposure at 20 mg/kg in terms of AUC_{0-48h} was 21125 ng·hr/mL when QTc prolongation first occurred, and was slightly lower than the steady state exposure (AUC_{ss} of 23800 ng·hr/mL) in patients at the recommended dose of 600 mg/day.
4) Analyzing FDA post-market data

Analyzing post-market adverse event to inform decision making
Example question

I am interested in developing new drugs acting on “Programmed death ligand-1 (PD-L1)” and “Programmed death receptor-1 (PD-1”).

What are the common observed post-market effects for drugs acting on these targets?

Impact: Competitive positioning and safety benchmarking
Summary table search

1. **Summary Table and Graphical View**
   - Select drugs of interest
   - Select adverse events (AEs) of interest
   - Start

   This new search type enables more advanced queries of FAERS reports.
   - Options include viewing FAERS reports:
     - Based on a group of drugs applying logic operators AND/OR/NOT
     - With comparative view of drugs in a summary table (e.g., view FAERS reports for a drug versus another drug).
     - With a graphical representation of the FAERS reports.
   - All types of searches include advanced filtering options (e.g., by

2. **Summary Table with Adverse Effects Tree (FAERS data)**

3. **Add Drugs**
   - PD
   - Add

   Each element from the following selection will be added as separate column:
   - Aliskizumab
   - Avelumab
   - Duralumab
   - Cameplimab
   - Nivolumab
   - Pembrolizumab

---

**ELSEVIER**
Sort the data

<table>
<thead>
<tr>
<th>Summary Table with Adverse Effects Tree</th>
<th>Atezolizumab</th>
<th>Avelumab</th>
<th>Durvalumab</th>
<th>Ceramlumab</th>
<th>Alizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>6625</td>
<td>1204</td>
<td>2310</td>
<td>154</td>
<td>46813</td>
</tr>
<tr>
<td>min &amp; max per column</td>
<td>1 - 1644</td>
<td>6 - 330</td>
<td>2 - 708</td>
<td>1 - 49</td>
<td>49 - 16720</td>
</tr>
<tr>
<td>+ Blood and lymphatic system disorders</td>
<td>881</td>
<td>128</td>
<td>197</td>
<td>20</td>
<td>12.99%</td>
</tr>
<tr>
<td>+ Cardiac disorders</td>
<td>541</td>
<td>90</td>
<td>170</td>
<td>11</td>
<td>7.14%</td>
</tr>
<tr>
<td>+ Congenital, familial and genetic disorders</td>
<td>2</td>
<td>12</td>
<td>2</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>+ Ear and labyrinth disorders</td>
<td>24</td>
<td>7</td>
<td>17</td>
<td>4</td>
<td>2.60%</td>
</tr>
<tr>
<td>+ Endocrine disorders</td>
<td>212</td>
<td>31</td>
<td>99</td>
<td>6</td>
<td>3.90%</td>
</tr>
<tr>
<td>+ Eye disorders</td>
<td>125</td>
<td>12</td>
<td>34</td>
<td>4</td>
<td>2.60%</td>
</tr>
<tr>
<td>+ Gastrointestinal disorders</td>
<td>1057</td>
<td>215</td>
<td>302</td>
<td>15</td>
<td>9.74%</td>
</tr>
<tr>
<td>+ General disorders and administration site conditions</td>
<td>1643</td>
<td>330</td>
<td>420</td>
<td>49</td>
<td>31.82%</td>
</tr>
</tbody>
</table>
Zoom in to relevant adverse effects

<table>
<thead>
<tr>
<th>Summary Table with Adverse Effects Tree (FAERS data)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data Display Options</strong></td>
</tr>
<tr>
<td><em>Show Results And Percentages</em></td>
</tr>
</tbody>
</table>

**Summary Table with Adverse Effects Tree**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Duvelumab</th>
<th>Camiplimab</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>27.41%</td>
<td>420</td>
<td>18.18%</td>
<td>49</td>
<td>31.82%</td>
</tr>
<tr>
<td><strong>Administration site reactions</strong></td>
<td>0.17%</td>
<td>13</td>
<td>0.50%</td>
<td>3</td>
<td>1.95%</td>
</tr>
<tr>
<td><strong>Body temperature conditions</strong></td>
<td>4.32%</td>
<td>97</td>
<td>4.20%</td>
<td>19</td>
<td>12.34%</td>
</tr>
<tr>
<td><strong>Complications associated with device</strong></td>
<td>0.00%</td>
<td>0</td>
<td>0.04%</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td><strong>Fatal outcomes</strong></td>
<td>5.73%</td>
<td>76</td>
<td>3.29%</td>
<td>6</td>
<td>3.90%</td>
</tr>
<tr>
<td><strong>Death and sudden death</strong></td>
<td>5.73%</td>
<td>76</td>
<td>3.29%</td>
<td>6</td>
<td>3.90%</td>
</tr>
<tr>
<td><strong>Brain death</strong></td>
<td>0.00%</td>
<td>0</td>
<td>0.00%</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td><strong>Cardiac death</strong></td>
<td>0.00%</td>
<td>0</td>
<td>0.00%</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>4.65%</td>
<td>73</td>
<td>3.16%</td>
<td>6</td>
<td>3.90%</td>
</tr>
<tr>
<td><strong>Death neonatal</strong></td>
<td>0.08%</td>
<td>0</td>
<td>0.00%</td>
<td>0</td>
<td>0.00%</td>
</tr>
</tbody>
</table>
Switch to graphical view
Examples addressed

1. **Full text searching**: Retrieving regulatory insights from hard-to-access regulatory documents
2. **Retrieving safety data**: Accessing high quality safety data extracted from literature and regulatory documents
3. **Analyzing FDA post-market data**: Analyzing post-market adverse event to inform decision making
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- Unique content
- High quality data
- Expert taxonomies
- Easy retrieval

Unprecedented access to preclinical and clinical information to make informed drug development decisions
5) Q&A
Leverage Pharmacokinetic data in PharmaPendium to inform drug development strategies

Informed decision making throughout Pharmaceutical development

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13 Nov 3pm CET/ 9 am EST
https://www.brighttalk.com/webcast/16527/373964
Thank you

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