High-Throughput CYP Inhibition Screening with Drug Probe Substrates: The RapidFire® Advantage

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BD Gentest® Contract Research Services

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Presentation Overview

• What makes a robust CYP inhibition assay?
• What is RapidFire®?
• CYP inhibition assay comparison
  – LC/MS vs RapidFire-MS
• Drug Discovery ADME Services from BD GentestSM
  Contract Services
Recent Example of CYP DDI-Tamoxifen and SSRI Interaction

- Retrospective analysis of 1300 breast cancer patients ca. 2003-2005

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tamoxifen with CYP2D6 inhibitor (n=353), %</th>
<th>Tamoxifen w/o CYP2D6 inhibitor (n=945), %</th>
<th>Adjusted odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer recurrence</td>
<td>13.9</td>
<td>7.5</td>
<td>1.9</td>
</tr>
</tbody>
</table>

- Analysis of subset of patients taking SSRI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tamoxifen with potent/moderate CYP2D6 inhibitors Fluoxetine, Paroxetine, Sertraline (n=213), %</th>
<th>Tamoxifen with weak CYP2D6 inhibitors citalopram, escitalopram, fluvoxamine (n=137), %</th>
<th>Adjusted odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer recurrence</td>
<td>16</td>
<td>Not statistically different than patients not taking inhibitor</td>
<td>~1.9</td>
</tr>
</tbody>
</table>

Potential Mechanism of Tamoxifen-SSRI Interaction

- Tamoxifen itself is a prodrug, converted by CYP2D6 into 4-hydroxytamoxifen (Dehal & Kupfer, 1997)
- 4-hydroxytamoxifen has 100X more affinity for ER than parent tamoxifen.
- Fluoxetine, Paroxetine, Sertraline
  - Well established, potent inhibitors of CYP2D6
  - IC$_{50}$ values often < 1 µM
Characteristics of Robust P450 Inhibition Assays

• Reaction must be single P450 isoform-specific
  • Use “probe” substrate with enzyme source (typically human liver microsomes or BD Supersomes™)
• Rapid metabolism of substrate
  • Get more metabolite, faster
• Short incubation time
  • Reduce substrate and inhibitor depletion (that can lead to artifacts)
  • Improves sensitivity in detecting time-dependent inhibitors
• Low protein concentration
  • ≤ 0.3 mg/mL
  • Reduce nonspecific binding to microsomes (that can lead to artifacts)
• Metabolite formation linear with:
  • Incubation time
  • Microsomal protein concentration
• Result is scalable across discovery and development
Guidance for Industry – Sept, 2006

<table>
<thead>
<tr>
<th>CYP</th>
<th>Substrate Preferred</th>
<th>Substrate Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>phenacetin-O-deethylation</td>
<td>7-ethoxyresorufin-O-deethylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>theophylline-N-demethylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>caffeine-3-N-demethylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tacrine 1-hydroxylation</td>
</tr>
<tr>
<td>2A6</td>
<td>coumarin-7-hydroxylation</td>
<td>nicotine C-oxidation</td>
</tr>
<tr>
<td>2B6</td>
<td>efavirenz hydroxylation</td>
<td>propofol hydroxylation</td>
</tr>
<tr>
<td></td>
<td>bupropion-hydroxylation</td>
<td>S-mephenytoin-N-demethylation</td>
</tr>
<tr>
<td>2C8</td>
<td>Taxol 6α-hydroxylation</td>
<td>amodiaquine N-demethylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rosiglitazone para-hydroxylation</td>
</tr>
<tr>
<td>2C9</td>
<td>tolbutamide methyl-hydroxylation</td>
<td>flurbiprofen 4'-hydroxylation</td>
</tr>
<tr>
<td></td>
<td>S-warfarin 7-hydroxylation</td>
<td>phenytoin-4-hydroxylation</td>
</tr>
<tr>
<td></td>
<td>diclofenac 4'-hydroxylation</td>
<td></td>
</tr>
<tr>
<td>2C19</td>
<td>S-mephenytoin 4'-hydroxylation</td>
<td>omeprazole 5-hydroxylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fluoxetine O-dealkylation</td>
</tr>
<tr>
<td>2D6</td>
<td>(±)-bufuralol 1'-hydroxylation</td>
<td>debrisoquine 4-hydroxylation</td>
</tr>
<tr>
<td></td>
<td>dextromethorphan O-demethylation</td>
<td></td>
</tr>
<tr>
<td>2E1</td>
<td>chlorzoxazone 6-hydroxylation</td>
<td>p-nitrophenol 3-hydroxylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lauric acid 11-hydroxylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>aniline 4-hydroxylation</td>
</tr>
<tr>
<td>3A4/5*</td>
<td>midazolam 1-hydroxylation</td>
<td>erythromycin N-demethylation</td>
</tr>
<tr>
<td></td>
<td>testosterone 6β -hydroxylation</td>
<td>dextromethorphan N-demethylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>triazolam 4-hydroxylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>terfenadine C-hydroxylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nifedipine oxidation</td>
</tr>
</tbody>
</table>

* Recommend use of 2 structurally unrelated CYP3A4/5 substrates for evaluation of in vitro CYP3A inhibition. If the drug inhibits at least one CYP3A substrate in vitro, then in vivo evaluation is warranted.
Ideal High Throughput Method...

- Methodology is similar to that used in drug development
  - No need to re-validate the approach
  - Chemists are more likely to believe and use the data
  - Conforms to FDA guidance (drug probes)
Ideal High Throughput Method (cont.)

• No pooling (prior to or after incubation)
  • Avoids substrate-substrate interactions
  • No need to re-validate the approach
  • Flexibility to optimize incubation time and protein
  • Obviates need to deconvolute data
  • Maintains analytical robustness
In a CRO...

- The CRO should meet expectations for:
  - Data reliability
  - Value
  - Turnaround time
BD Biosciences – RapidFire Partnership

The in vitro ADME market leader in products and services, BD Biosciences, and a technology leader in high-throughput LC/MS, BIOCIUS Life Sciences, combine to provide a complete service package for cytochrome P450 inhibition.

BD Biosciences’ validated assay methods combined with RapidFire high throughput LC-MS/MS technology.
RapidFire Mass Spectrometry

- RapidFire from BIOCIUS
- Replaces the LC of LC/MS with a rapid sample purification system
- Micro scale solid-phase extraction (μSPE)
- Isocratic run
- 5-8 sec cycle times
- No sample prep
- **Permits ultra-rapid data turnaround!**

RapidFire 300 for in vitro ADME
d4-1'-OH-midazolam internal standard (100 nM)

Raw Data: 96-well plates on Agilent-6410
96-well plate analyzed in under 12 minutes

1'-OH-midazolam product
How We Validated Our Assays and How We Conduct Them for Clients - Using Conventional LC/MS
Optimization of Metabolite Formation with Time & Protein

- Linearity of metabolite formation with incubation time and HLM protein concentration
- Remember, \( v \sim [S] \)
- “Preferably no more than 10-30% substrate or inhibitor depletion should occur.” – FDA guidance

0.1 mg/mL 10 min 27% [S] depletion

0.05 mg/mL 6 min 34% [S] depletion
Example Assay Validation Data Set: Diclofenac 4’-hydroxylase

- Resulting Data Set
  - $K_M$ determination
    - 3.5 µM, 3.9 µM
  - $IC_{50}$ and $K_i$ determination w. sulfaphenazole
    - $IC_{50}$: 0.41 µM, 0.63 µM
    - $K_i$: 0.20 µM, 0.19 µM
# Cytochrome P450 Inhibition Assay Parameters

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>K_M</th>
<th>Model</th>
<th>[S]</th>
<th>Inc time (min)</th>
<th>HLM (mg/mL)</th>
<th>Analytical method</th>
<th>Competitive inhibitor</th>
<th>Time Dependent inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Phenacetin</td>
<td>37</td>
<td>MM</td>
<td>40</td>
<td>10</td>
<td>0.2</td>
<td>LC/MS</td>
<td>α-Naphthoflavone</td>
<td>Furafylline</td>
</tr>
<tr>
<td>CYP2A6</td>
<td>Coumarin</td>
<td>1.3</td>
<td>MM</td>
<td>1.5</td>
<td>5</td>
<td>0.05</td>
<td>LC/MS</td>
<td>Tranylcypromine</td>
<td>8-Methoxypsoralen</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Bupropion</td>
<td>79</td>
<td>MM</td>
<td>80</td>
<td>10</td>
<td>0.1</td>
<td>LC/MS</td>
<td>Ketoconazole</td>
<td>Ticlopidine</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>Amodiaquine</td>
<td>1.1</td>
<td>MM</td>
<td>2</td>
<td>5</td>
<td>0.02</td>
<td>LC/MS</td>
<td>Montelukast</td>
<td>Gemfibrozil-gluc</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Diclofenac</td>
<td>3.7</td>
<td>MM</td>
<td>5</td>
<td>5</td>
<td>0.05</td>
<td>LC/MS</td>
<td>Sulfaphenazole</td>
<td>Tienilic acid</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>S-mephenytoin</td>
<td>43</td>
<td>MM</td>
<td>40</td>
<td>10</td>
<td>0.3</td>
<td>LC/MS</td>
<td>S-Benzylirvanol</td>
<td>S-fluoxetine</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Dextromethorphan</td>
<td>4.9</td>
<td>MM</td>
<td>5</td>
<td>5</td>
<td>0.1</td>
<td>LC/MS</td>
<td>Quinidine</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Chlorzoxazone</td>
<td>60</td>
<td>MM</td>
<td>60</td>
<td>5</td>
<td>0.1</td>
<td>LC/MS</td>
<td>Chloromethiazole</td>
<td>Diethylthiocarbamate</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Midazolam</td>
<td>2.2</td>
<td>MM</td>
<td>3</td>
<td>5</td>
<td>0.02</td>
<td>LC/MS</td>
<td>Ketoconazole</td>
<td>Azamulin</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Testosterone</td>
<td>65</td>
<td>Hill</td>
<td>50</td>
<td>10</td>
<td>0.05</td>
<td>LC/MS</td>
<td>Ketoconazole</td>
<td>Azamulin</td>
</tr>
</tbody>
</table>

1 – K_s, Hill coefficient n = 1.3

- Parameters validated: Linearity of metabolite formation with time & protein, K_M, IC_{50}, TDI
- Aligned with FDA guidance: Drug-drug interaction studies (Sept, 2006)
## Validated Analytical Methods

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>Metabolite</th>
<th>Mass Transition</th>
<th>Internal Standard</th>
<th>Mass Transition</th>
<th>Ionization</th>
<th>LLOQ (µM)</th>
<th>Std. Curve Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Phenacetin</td>
<td>Acetaminophen</td>
<td>151 → 111</td>
<td>Acetaminophen-[(^{13})C(_2)^{15})N]</td>
<td>155 → 110</td>
<td>ESI+</td>
<td>0.0760</td>
<td>0.076-5.0</td>
</tr>
<tr>
<td>CYP2A6</td>
<td>Coumarin</td>
<td>7-hydroxycoumarin</td>
<td>161 → 133</td>
<td>7-OH-Coumarin-[D(_3)]</td>
<td>166 → 138</td>
<td>ESI-</td>
<td>0.0020</td>
<td>0.002-1.0</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Bupropion</td>
<td>Hydroxybupropion</td>
<td>256 → 139</td>
<td>Hydroxybupropion-[D(_6)]</td>
<td>262 → 244</td>
<td>ESI+</td>
<td>0.0005</td>
<td>0.0005-0.8</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>Amodiaquine</td>
<td>Des-ethyl amodiaquine</td>
<td>328 → 283</td>
<td>Des-ethyl amodiaquine-[D(_3)]</td>
<td>331 → 283</td>
<td>ESI+</td>
<td>0.0047</td>
<td>0.0047-1.5</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Diclofenac</td>
<td>4′-OH Diclofenac</td>
<td>312 → 268</td>
<td>4′-OH Diclofenac-[(^{13})C(_6)]</td>
<td>316 → 272</td>
<td>ESI-</td>
<td>0.0087</td>
<td>0.0087-2.0</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>S-mephenytoin</td>
<td>4′-OH S-Mephenytoin</td>
<td>235 → 150</td>
<td>4′-OH S-Mephenytoin-[D(_3)]</td>
<td>238 → 150</td>
<td>ESI+</td>
<td>0.0040</td>
<td>0.004-10.0</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Dextromethorphan</td>
<td>Dextrophan</td>
<td>258 → 157</td>
<td>Dextrophan-[D(_3)]</td>
<td>261 → 157</td>
<td>ESI+</td>
<td>0.0025</td>
<td>0.0025-1.0</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Chlorzoxazine</td>
<td>6-OH Chlorzoxazine</td>
<td>184 → 120</td>
<td>6-OH Chlorzoxazine-[D(_2)^{15})N]</td>
<td>187 → 67</td>
<td>ESI-</td>
<td>0.0022</td>
<td>0.0022-20.0</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Midazolam</td>
<td>1′-OH Midazolam</td>
<td>342 → 203</td>
<td>1′-OH Midazolam-[(^{13})C(_3)]</td>
<td>347 → 208</td>
<td>ESI+</td>
<td>0.0025</td>
<td>0.0025-1.0</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Testosterone</td>
<td>6β-OH Testosterone</td>
<td>305 → 269</td>
<td>6β-OH Testosterone-[D(_7)]</td>
<td>312 → 276</td>
<td>ESI+</td>
<td>0.0160</td>
<td>0.016-10.0</td>
</tr>
</tbody>
</table>

- Parameters validated: Selectivity, Standard curve and QC sample Accuracy and Precision, Carryover, Stability, Autosampler stability, LLOQ
- Full accordance with FDA guidance document for analytical method validation (2001)
- Matrix: 0.1 mg/mL HLM, NADPH regenerating system
IC$_{50}$ and K$_i$ Values Obtained With Conventional LC/MS

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>Inhibitor</th>
<th>mean IC$_{50}$ (nM)</th>
<th>mean K$_i$ (nM)</th>
<th>Best fit model</th>
<th>ratio IC$_{50}$/K$_i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Phenacetin</td>
<td>7,8-Benzoﬂavone</td>
<td>9</td>
<td>3</td>
<td>Mixed</td>
<td>2.7</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Bupropion</td>
<td>Ketoconazole</td>
<td>2250</td>
<td>1400</td>
<td>Competitive</td>
<td>1.6</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>Amodiaquine</td>
<td>Montelukast</td>
<td>22</td>
<td>13</td>
<td>Competitive</td>
<td>1.7</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Diclofenac</td>
<td>Sulfaphenazole</td>
<td>520</td>
<td>195</td>
<td>Competitive</td>
<td>2.7</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>(S)-Mephenytoin</td>
<td>(S)-Benzynirvanol</td>
<td>410</td>
<td>340</td>
<td>Competitive</td>
<td>1.2</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Dextromethorphan</td>
<td>Quinidine</td>
<td>62</td>
<td>50</td>
<td>Competitive</td>
<td>1.2</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Midazolam</td>
<td>Ketoconazole</td>
<td>16</td>
<td>9</td>
<td>Mixed</td>
<td>1.8</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Testosterone</td>
<td>Ketoconazole</td>
<td>19</td>
<td>21</td>
<td>Competitive</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Values represent means of two independent determinations; Global CV = 0.13

Extensive experimental detail available in the following publication:


Mean = 1.7
How We Validated Our Assays and How We Conduct Them for Clients – Using RapidFire MS
Assay Methods for RapidFire Analysis

- Assay are conducted in an identical manner
- No add’l validation, except CYP1A2 and CYP2B6 (next slides)
Tacrine Used as the Probe for CYP1A2

- Tacrine used as an alternate to phenacetin
- In-source fragmentation
- Tacrine is also FDA-recommended

![Chemical Structure of Tacrine](image)

![Graph showing product formed vs. log(Furafylline) concentration](image)
CYP2B6 - Bupropion

- Criteria – 5 fold s/n at the IC$_{50}$
- Boosted the protein concentration (0.2 mg/mL)
- Extended the incubation time (20 min)
Comparison of RapidFire with Conventional

- To compare performance:
  - We generated full, 7 point IC$_{50}$ curves
  - Multiple compounds
  - 7 enzymes, 8 substrates
- Samples were split
- Analyzed at BD and at BIOCIUS
- Results to follow:
Results

- N = 43 IC$_{50}$ curves
- R-squared = 0.97
- No systematic bias
  - Ratio of RapidFire to Conventional = 1.13

Data from 8 different enzyme/substrate pairs and 1 to 3 inhibitors for each pair. Inhibitors include ketoconazole, α-naphthoflavone, montelukast, S-benzynirvanol, sulfaphenazole, azamulin, paroxetine, ticlopidine, S-fluoxetine, tienilic acid, verapamil and diltiazem, tamoxifen, ritonavir, erythromycin, mibefradil.
Analysis of Ritonavir by IC$_{50}$ Shift – Midazolam as Substrate for CYP3A4

- **IC$_{50}$ - RapidFire**
  - w/ NADPH = 11 nM
  - w/o NADPH = 24 nM
  - Shift = 2.17

- **IC$_{50}$ - Conventional**
  - w/ NADPH = 11 nM
  - w/o NADPH = 22 nM
  - Shift = 2.04

IC$_{50}$ shift with dilution to mimic recommended $K_i/k_{inact}$ study design (Grimm et al, 2009)
Analysis of Ritonavir by IC₅₀ Shift – Testosterone as Substrate for CYP3A4

- **IC₅₀ - RapidFire**
  - w/ NADPH = 4.4 nM
  - w/o NADPH = 11 nM
  - Shift = 2.47

- **IC₅₀ - Conventional**
  - w/ NADPH = 3.9 nM
  - w/o NADPH = 9.4 nM
  - Shift = 2.40

IC₅₀ shift with dilution to mimic recommended Kᵢ/Kᵢ₉₅ inactive study design (Grimm et al, 2009)
# Inter- and Intraplate Reproducibility in IC$_{50}$ Values

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intraplate CV</th>
<th>Interplate CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4/ Midazolam/ Ketoconazole</td>
<td>0.29</td>
<td>0.28</td>
</tr>
</tbody>
</table>

N = 36 IC$_{50}$ values; mean = 17 nM
Examination of Analytical Selectivity in the Absence of Chromatography

Testosterone Metabolism as a Case Study
Selectivity of Testosterone

- Testosterone is a major CYP3A4 probe
  - Hydroxytestosterone metabolites yield essentially identical fragmentation by MS
  - With conventional LC/MS, chromatography solves this issue
- RapidFire-MS uses a µSPE cartridge for sample clean up.
  - There is ~ no chromatographic separation of analytes
- Does MRM alone provide adequate selectivity?
  - Non-6β-OH metabolites may be confounders

Conditions: 250 µM testosterone, 0.1 mg/mL
10 min. Red trace is 6β-OH Testosterone-[D7]
Review of Testosterone Metabolism In Vitro

- Multiple hydroxylated metabolites in HLM
  - 6β, 2β, 1β, 15β, 16β, 11β, 2α(?) [(Waxman et al (1988); Krauser et al (2004); Choi et al (2005)]

- 85-90% of total is 6β-OH
- ~10% is 2β-OH
- CYP3A4 > to >> 2C9, 2C19 for all
- There is a very minor contribution of non-CYP3A4 to total response
Potential Impact of Selectivity of CYP Probe Substrate

- CYP probe substrates are generally selective but not specific in HLM.
- Model decreasing selectivity
- Any decrease in selectivity tends to increase IC\textsubscript{50} values.

![Graph showing percent activity vs. substrate selectivity and IC\textsubscript{50} values.]

<table>
<thead>
<tr>
<th>Substrate Selectivity</th>
<th>Relative IC\textsubscript{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>1.00</td>
</tr>
<tr>
<td>90</td>
<td>1.28</td>
</tr>
<tr>
<td>80</td>
<td>2.06</td>
</tr>
<tr>
<td>70</td>
<td>3.58</td>
</tr>
</tbody>
</table>
Correlation Analysis – CYP3A4/testosterone

R² = 0.995

IC₅₀ (uM) by Traditional LCMS @ BD Gentest vs. IC₅₀ (uM) by RapidFire @ BioTrove

Inhibitors tested: Ketoconazole, Fluoxetine, Ritonavir, Azamulin, Mibebradil, Verapamil, Diltiazem
The BD-BIOCIUS Advantage

• Features
  – Full 7-point IC$_{50}$ curves
    • Single point, percent inhibition is risky – especially for CYP3A4
  – MS with stable-labeled isotopes
  – Individually incubated and analyzed
  – Uses BD UltraPool HLM 150™ human liver microsomes or your company’s pool
  – GLP- Validated Assay Methodology - in Drug Discovery!

• Complete sample preparation and data analysis
  – Customers provide compounds to BD, we conduct incubations, BIOCIUS performs analysis - BD provides completed data package to customer

• Rapid Turnaround
  – Data available in 1 week

• Cost-effective
  – $250 per 7 point curve

• Time-dependent inhibition assays available
BD Gentest Contract Services

- We offer a full spectrum of affordable, high throughput ADME Drug Discovery services
  - CYP inhibition by RapidFire
  - Metabolic stability in microsomes
  - Metabolic stability in hepatocytes
  - Plasma protein binding (Rapid Equilibrium Dialysis)
  - HT-reaction phenotyping with BD Supersomes™
  - Caco-2 or MDR1-LLC-PK1 monolayers
  - Solubility

- BD UltraPool™ HLM 150 application
Come visit us in Woburn, MA USA
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Questions?

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