Discovering and Developing the Best Candidates for LA/ER Administration: What the Industry Looks For

Magali Hickey

LA/ER ARV Workshop

February 22nd, 2015
Alkermes: A Global Biopharmaceutical Company

- Diversified portfolio of more than 20 commercial products
- Headquartered in Dublin, Ireland
- R&D in Waltham, MA
- R&D and Mfg. in Athlone, Ireland
- Manufacturing facilities
  - Gainesville, GA
  - Wilmington, OH
- ~1250 employees
- NASDAQ: ALKS
Dynamic Portfolio with CNS Focus

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Filed</th>
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<tr>
<td>Aripiprazole Lauroxil (Schizophrenia LAI)</td>
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<td>INVEGA® SUSTENNA® 3-Month (Schizophrenia LAI)</td>
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<td>Eventide Once Weekly Suspension (Type 2 Diabetes)</td>
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<td>ALKS 5461 (Major Depressive Disorder)</td>
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<td>ALKS 7106 (Pain)</td>
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<td>RDB 1419 (Cancer)</td>
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</table>
Outline

- Introduction to Long-Acting Injectables (LAIs)
- Biopharmaceutics Considerations
- Case Studies
  - RISPERDAL® CONSTA®
  - INVEGA® SUSTENNA®
- Additional Considerations: Combination Product Regulations
- Summary
Examples of Long-Acting Injectables (LAI)
LAIs of ATAPs Improve Relapse Rates, Efficacy and Tolerability

A retrospective comparison of two-year data from patients with schizophrenic disorders treated with long-acting injectable risperidone vs. oral antipsychotics (haloperidol or risperidone)

These improved outcomes have been shown to result in significant pharmacoeconomic savings as well.

Fig. 1  Survival curve for patients treated with fluphenazine in the community (time to relapse): depot v. oral formulation. Reproduced with permission from Hogarty et al.22

Evolution of Atypical Antipsychotic LAIs

First-generation antipsychotics

- Oil solutions
- Polymer microspheres

Second-generation (Atypical) antipsychotics

- Crystalline drug in aqueous suspension

- ZYPREXA® RELPREVV®
- ABILIFY MAINTENA®
- RISPERDAL® CONSTA®
- INVEGA® SUSTENNA®
- Aripiprazole lauroxil

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Key Challenges

General guidelines outlining the design of bioequivalence programs for LAIs are not available
- Complex formulations with complex release profiles
- Product specific

Bridging clinical and “to be marketed” formulations
- Impact of small changes in formulation

Potential for dose dumping

IVIVC
- In vivo variability high; in vitro variability low
- Physiological or biorelevance of in vitro release methods

FDA bioequivalence recommendations for Specific Products (released from 2007 onwards).
Minutes and transcript for the April 13, 2010 Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee.
## Attributes Influencing Use and Performance: Biopharmaceutic Considerations for LAIs

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Impacts</th>
<th>Method</th>
<th>Measurement</th>
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<tbody>
<tr>
<td>Form</td>
<td>Dissolution/ solubility</td>
<td>Diffraction/ Spectroscopy (IR)</td>
<td>Direct</td>
</tr>
<tr>
<td>Morphology</td>
<td>Dissolution/ Processing</td>
<td>Scanning Electron Microscopy</td>
<td>Direct</td>
</tr>
<tr>
<td>Drug substance PSD</td>
<td>Dissolution</td>
<td>Laser diffraction</td>
<td>Indirect</td>
</tr>
<tr>
<td>Surface area of drug substance</td>
<td>Dissolution</td>
<td>Gas adsorption (BET)</td>
<td>Direct</td>
</tr>
<tr>
<td>PSD of drug product</td>
<td>Resuspension and injectability/ Dissolution</td>
<td>Laser diffraction</td>
<td>Indirect</td>
</tr>
<tr>
<td>Rheology</td>
<td>Mechanical reliability</td>
<td>Viscosity</td>
<td>Direct</td>
</tr>
<tr>
<td>Solubility</td>
<td>Dissolution/Potential for dose dumping</td>
<td>HPLC</td>
<td>Direct</td>
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</tbody>
</table>
What is Most Critical to Measure?

- Depends on mechanism of release
  - If governed by dissolution, PSD/surface area may be most relevant

- Animal models
  - Can be informative, especially in early stages of formulation design

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**Fig. 4.** Dissolution profiles of PP-NA and PP-NB (represented PP-NA; represented PP-NB).

**Fig. 7.** Plasma concentration-time curves for PP-NA and PP-NB following i.m. administrations of 117 mg PP in beagle dogs (data were expressed as mean ± SD, n = 6).
Dissolution as Link From Drug Substance to Drug Product

- Physicochemical properties of drug substance and drug product key to development of appropriate methods and specifications
- Correlation between physicochemical attributes and *in vitro* dissolution is critical
- *In vitro* dissolution methods should provide the link to *in vivo* performance
Dose Dumping: Olanzapine Pamoate

- Resulted in plasma concentrations much higher than expected
- Adverse event described as post-injection delirium sedation/syndrome (PDSS)
- Required patients to be monitored for 3 hours post injection
- “Burst” or “dump” occurs in <0.1% of injections
Intrinsic dissolution of olanzapine pamoate in plasma (0.73 mg/hr·cm²) was approximately 6 times higher than in the phosphate buffer (pH 7.46 = 0.12 mg/hr·cm²).

PDSS hypothesized to be related to exposure of product to a substantial volume of blood.

- Most likely the result of unintended partial intravascular injection or blood vessel injury during the injection.

**Related to Solubility?**

![Figure 4 Illustration of proposed mechanism for olanzapine LAI distribution (in yellow) after vessel damage by nicking.](http://www.biomedcentral.com/content/pdf/1471-244X-10-45.pdf)
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RISPERDAL® CONSTA®: Poly lactide-co-glycolide (PLGA) Based Microspheres

- Safe with extensive experience in humans
  - Hydrolyzes into lactic acid and glycolic acid which are normal by-products of various metabolic pathways in the body
  - Extensive use in humans (Sutures, orthopedics, bone plates, microspheres)

- Customizable for specific application
  - Lactide / Glycolide ratio
  - Molecular Weight
  - Hydrophobicity via end group selection (acid or ester)

- Low monomer option with purification
RISPERDAL® CONSTA®: Risperidone in Polymeric Microspheres

- Dry Powder microspheres + Diluent
- Microsphere suspension
- Hypodermic needle
- SC or IM
Microsphere Delivery System

- API with stabilizers and modifiers
- Biodegradable Polymer Matrix
- Pores
- Dense surface
- Excipient(s)

Size ranges from 25µm - 150µm
Medisorb®: Mechanism of Drug Release

- **HYDRATION**
  - Initial release

- **DRUG DIFFUSION**
  - Sustained release

- **POLYMER EROSION**

Diagram showing:
- Drug particle
- Polymer matrix
Resulting Molecular Weight Decrease and Drug Release

Phase 1 Release – Initial Release
First 24 hrs

Phase 2 Release – Hydration Phase
Day 2-15

Phase 3 Release – Primary Release Phase
Day 16-49

Initial Release (diffusion)  Sustained Release (polymer erosion)

Polymers Mw (kD)

% Release

Days
The overall duration of release can be modulated from weeks to months by altering the Lactide: Glycolide ratio.
The overall duration of release increases with increase in molecular weight within a L:G ratio.

The release profile may be ‘tailored’ by selecting polymer with appropriate L:G ratio and Molecular Weight.
Effect of Particle Size

- Particle size does not influence release rates—consistent with mechanism of release
When mechanism of release is understood, studies towards establishing IVIVC are possible.

Animal studies are informative but only human data permit regulatory definitions of IVIVC.

- Level A: Point to point comparison
- Level B: The mean in vitro dissolution time is compared either to the mean residence time or to the mean *in vivo* dissolution time
- Level C: single point relationship between a dissolution parameter (e.g. \( t_{50\%} \) dissolved in 4 hours) and a pharmacokinetic parameter (e.g., AUC, \( C_{\text{max}} \), \( T_{\text{max}} \))
INVEGA® SUSTENNA® BA/BE Study

- Mechanism of release: crystal dissolution
- Surface area range covered: 2 to 12 m²/g
- In addition to evaluating the impact of surface area on PK, the addition of citric acid was further tested to bridge clinical formulation and “to be marketed” formulation (treatment F)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Drug product</th>
<th>Specific Surface Area (m²/g)</th>
<th>Release Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Solution</td>
<td>NA</td>
<td>Immediate release</td>
</tr>
<tr>
<td>B</td>
<td>Nanosuspension</td>
<td>~2</td>
<td>Extra slow</td>
</tr>
<tr>
<td>C</td>
<td>Nanosuspension</td>
<td>5-7</td>
<td>Slow</td>
</tr>
<tr>
<td>D</td>
<td>Nanosuspension (no citric acid)</td>
<td>~9.5</td>
<td>Intermediate</td>
</tr>
<tr>
<td>E</td>
<td>Nanosuspension</td>
<td>12</td>
<td>Fast</td>
</tr>
<tr>
<td>F</td>
<td>Nanosuspension (with citric acid)</td>
<td>~9.5</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf © 2015 Alkermes. All rights reserved.
PK Parameters

A comparison of the PK parameters of different treatments with 50 mg eq. paliperidone palmitate is given in Table below.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Extra Slow (F013) (B)</th>
<th>Slow (F013) (C)</th>
<th>Intermediate (F013) (D)</th>
<th>Fast (F013) (E)</th>
<th>Intermediate (F013) (F)</th>
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<tr>
<td>$C_{\text{max}}$, ng/mL</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
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<tr>
<td></td>
<td>4.39 ± 3.03 (n=29)</td>
<td>7.36 ± 3.16 (n=22)</td>
<td>9.91 ± 5.59 (n=25)</td>
<td>12.80 ± 9.08 (n=26)</td>
<td>9.54 ± 5.99 (n=23)</td>
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<td></td>
<td>3.62</td>
<td>7.27</td>
<td>9.40</td>
<td>9.66</td>
<td>7.82</td>
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<td>$t_{\text{max}}$, days</td>
<td>Median (min - max)</td>
<td>Median (min - max)</td>
<td>Median (min - max)</td>
<td>Median (min - max)</td>
<td>Median (min - max)</td>
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<tr>
<td></td>
<td>29.00 (3.05 - 55.02)</td>
<td>16.00 (4.03 - 42.04)</td>
<td>12.07 (3.00 - 49.00)</td>
<td>11.50 (2.00 - 34.00)</td>
<td>12.07 (6.00 - 49.00)</td>
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<tr>
<td></td>
<td>4809</td>
<td>9677</td>
<td>8176</td>
<td>10921</td>
<td>8550</td>
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<tr>
<td>$AUC_{\text{last}}$, ng.h/mL</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
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<td></td>
<td>5595 ± 3668 (n=35)</td>
<td>9039 ± 2948 (n=23)</td>
<td>9317 ± 4005 (n=25)</td>
<td>11228 ± 3494 (n=26)</td>
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<td>4809</td>
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<td>8176</td>
<td>10921</td>
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<tr>
<td>$t_{\text{last}}$, days</td>
<td>Median (min - max)</td>
<td>Median (min - max)</td>
<td>Median (min - max)</td>
<td>Median (min - max)</td>
<td>Median (min - max)</td>
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<td>139.00 (10.00 - 259.00)</td>
<td>125.00 (58.08 - 127.08)</td>
<td>125.00 (62.00 - 127.05)</td>
<td>125.03 (41.00 - 134.04)</td>
<td>125.00 (58.00 - 130.04)</td>
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<td>apparent $t_{1/2}$, days</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
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<td>35.00 ± 20.40 (n=24)</td>
<td>27.66 ± 10.11 (n=13)</td>
<td>35.27 ± 12.01 (n=17)</td>
<td>29.90 ± 13.20 (n=21)</td>
<td>28.15 ± 10.58 (n=17)</td>
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<td>30.70</td>
<td>24.04</td>
<td>34.38</td>
<td>29.89</td>
<td>30.45</td>
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<td>$AUC_{\infty}$, ng.h/mL</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
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<td>6828 ± 3800 (n=24)</td>
<td>10303 ± 1912 (n=13)</td>
<td>11992 ± 4531 (n=17)</td>
<td>12901 ± 3335 (n=21)</td>
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<td>7111</td>
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PK Parameters http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf © 2015 Alkermes. All rights reserved.
IVIVC Results

- Predicted vs. observed median paliperidone pharmacokinetics
- Original model was challenged by reviewer due to high variability in clinical data
  - Low variability *in vitro*, as expected
  - Reviewer replotted data
- Despite high degree of variability, level A IVIVC was demonstrated

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf
It is noted that not only the *in vivo* variability is large, but also the relationship between *in vitro* and *in vivo* is not linear if it exists.

- Therefore, the applicant’s approaches seem reasonable by using nonlinear model and by using NONMEM program to take the variability into consideration.

What about dissolution and specifications?

12. Is the proposed dissolution specification adequate?

Based on the developed and validated Level A IVIVC model for paliperidone palmitate, the following in-vitro release specifications are proposed. The 8-minute time point (b) (4) the 20-minute time point monitors the (b) (4) and the 45-minute time point assesses (b) (4) has been released. The proposed in vitro release specification ranges are shown in Table below.

Clinical data will be used to support and justify specifications.
Relative BA: Bridging Clinical and “To Be Marketed” Formulations

- Both formulations were used in Phase 3; The only difference was the addition of citric acid to the “to be marketed” formulation
- “Although the point estimates suggest that paliperidone exposure (AUC, Cmax) are similar for both formulations, the bioequivalence was not shown.”

![Table Image]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Group</th>
<th>N</th>
<th>Geometric L.S. Means(*)</th>
<th>90% CI</th>
<th>Estimated Ratio (F013/F011)(*)</th>
<th>90% CI</th>
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<tbody>
<tr>
<td>AUC&lt;sub&gt;0-648h&lt;/sub&gt;</td>
<td>INTERMEDIATE</td>
<td>25</td>
<td>3582.75</td>
<td>(2920.94; 4394.51)</td>
<td>91.58</td>
<td>(68.40; 122.61)</td>
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<td>F013 (D)</td>
<td></td>
<td>3912.11</td>
<td>(3176.06; 4818.75)</td>
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<tr>
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<td>INTERMEDIATE</td>
<td>24</td>
<td>8491.88</td>
<td>(7376.37; 9776.09)</td>
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<tr>
<td></td>
<td>F011 (F)</td>
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<td>9063.19</td>
<td>(7849.80; 10464.14)</td>
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<tr>
<td>AUC&lt;sub&gt;last&lt;/sub&gt;</td>
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<td>F013 (D)</td>
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<td>9063.19</td>
<td>(7849.80; 10464.14)</td>
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<tr>
<td></td>
<td>INTERMEDIATE</td>
<td>24</td>
<td>11259.88</td>
<td>(9720.37; 13043.21)</td>
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<td>F011 (F)</td>
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<td>10707.18</td>
<td>(9243.23; 12402.97)</td>
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<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt;</td>
<td>INTERMEDIATE</td>
<td>17</td>
<td>8.40</td>
<td>(6.90; 10.22)</td>
<td>105.16</td>
<td>(85.42; 129.47)</td>
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<td>F013 (D)</td>
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<td>8.40</td>
<td>(6.90; 10.22)</td>
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<tr>
<td></td>
<td>INTERMEDIATE</td>
<td>17</td>
<td>8.17</td>
<td>(6.66; 10.03)</td>
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<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
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<td>25</td>
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<td>(6.90; 10.22)</td>
<td>102.77</td>
<td>(77.38; 136.48)</td>
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<td>(6.66; 10.03)</td>
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<td>8.17</td>
<td>(6.66; 10.03)</td>
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</tbody>
</table>

(*) Data analyzed on log scale, but statistics transformed back to original scale

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf © 2015 Alkermes. All rights reserved.
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- Summary
Additional Considerations: Drug Device Combination Products

- Defined as combination of:
  - Drug Product
  - Device
- Need to demonstrate and validate that the end-user can “safely and effectively” use the product
  - Significant emphasis on reduction of risk that may lead to medication errors
- Validation according to principles of Human Factors Engineering
### Regulatory Guidance: Drug and Device Divisions

<table>
<thead>
<tr>
<th>Source</th>
<th>Final or Draft Guidance Document Titles</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDER</td>
<td>Safety Consideration for Product Design to Minimize Medication Errors Guidance (December 2012); Part 1: Container Closure System</td>
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<tr>
<td>CDER</td>
<td>Safety Consideration for Product Design to Minimize Medication Errors Guidance (April 2013); Part 2: Label and Labeling</td>
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<tr>
<td>CDRH</td>
<td>Applying Human Factors &amp; Usability Engineering to Optimize Medical Device Design (June 2011)</td>
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<tr>
<td>CDRH</td>
<td>Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management (July 2000)</td>
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<tr>
<td>ISO 11040-6</td>
<td>Part 6: Plastic barrels for injectables</td>
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<tr>
<td>CDER, CDRH, CBER, and OCP</td>
<td>Technical considerations for Pen, Jet and Related Injectors Intended for Use with Drugs and Biological Products (April 2009)</td>
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<tr>
<td>OCP</td>
<td>Current GMP Practice for Combination Products (September 2004)</td>
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</table>
Summary

- Long-acting injectable products of atypical antipsychotics improve efficacy and increase patient compliance
- Biopharmaceutics approach in all stages of development will facilitate registration of these products
- IVIVC for LAIs is possible, even if clinical variability is high
- Special consideration to device and combination product guidance is required to ensure the intended user can safely and effectively use the product
Many thanks to colleagues at Alkermes that contributed to this presentation

Thank you!

Questions?