Industry Potential Interest Conflicts

- **Employer:** Employed by and have equity in ICPD, a company that provides pharmacometric services to industry.

- **Financial Interests or Benefits:** Achaogen, Actelion, AiCuris, Arsanis, Basilea, Cellceutix, Cempra, Cidara, Contrafect, Debiopharm, Geom, GSK, Insmed, Kalya, Medicines Company, Meiji, Melinta, Merck, Nabriva, Nexcida, Northern Antibiotics, Novartis, Paratek, Roche, Spero, Takeda, Theravance, Tetraphase, VenatoRx, Wockhardt, Zavante.

- **Speaker’s Bureau:** None

Government Potential Interest Conflicts

- **Special Government Employee, FDA:** Anti-infective Advisory Committee, temporary member.

---

Paul G. Ambrose, Pharm.D., FIDSA
Pharmacometric Considerations in Unmet Need Programs

18 July 2016

Paul G. Ambrose, Pharm.D., FIDSA

Institute for Clinical Pharmacodynamics, Inc.
Schenectady, New York
Antibiotic development program failure is less about bad drugs and more about bad decisions.
Superiority can be found on an exposure-response function
Could failure have been predicted?
Daptomycin

EXPOSURE IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA


FATAL MISTAKE: WRONG ANIMAL MODEL


Tigecycline

EXPOSURE-RESPONSE IN MICE

Preclinical data: Courtesy of William A. Craig
Tigecycline

EXPOSURE IN PATIENTS WITH HOSPITAL-ACQUIRED PNEUMONIA

Preclinical data: Courtesy of William A. Craig


FATAL MISTAKE:
MAXIMUM TOLERATED DOSE INSUFFICIENT

Preclinical data: Courtesy of William A. Craig


EXPOSURE IN PATIENTS WITH HOSPITAL-ACQUIRED PNEUMONIA


Ceftobiprole

\[ r^2 = 0.84 \]

Change in Log_{10} CFU in Thigh at 24h

Free-Drug % Time > MIC

HABP + VABP
FATAL MISTAKE: ELF PENETRATION NOT ACCOUNTED FOR

**Ceftobiprole**


EXPOSURE IN PATIENTS WITH HOSPITAL-ACQUIRED PNEUMONIA

Doripenem


FATAL MISTAKE: DRUG CLEARANCE IN VAP PATIENTS NOT ACCOUNTED FOR


EXPOSURE-RESPONSE IN MICE

EXPOSURE IN PATIENTS WITH HOSPITAL-ACQUIRED PNEUMONIA


SUCCESS PREDICTABLE

New Drug Applications

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Target Attainment Median (Range)</th>
<th>% NDA Approval (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.62 (0.01-0.76)</td>
<td>40% (2/5)</td>
</tr>
<tr>
<td>2</td>
<td>0.85 (0.77-0.88)</td>
<td>60% (3/5)</td>
</tr>
<tr>
<td>3</td>
<td>0.94 (0.88-0.96)</td>
<td>80% (4/5)</td>
</tr>
<tr>
<td>4</td>
<td>0.985 (0.97-0.99)</td>
<td>100% (5/5)</td>
</tr>
</tbody>
</table>

20 pneumonia programs; 17 antibiotics in total, with 14 regulatory approvals and 6 failures

How to keep the NDA on the tracks?
A Proven Approach

Pathogen susceptibility: Patient population matters

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>Percent Susceptible, HABP/VABP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td></td>
<td>Klebsiella species</td>
</tr>
<tr>
<td></td>
<td>Acinetobacter species</td>
</tr>
<tr>
<td></td>
<td>Enterobacter species</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>72/66</td>
</tr>
<tr>
<td></td>
<td>82/71</td>
</tr>
<tr>
<td></td>
<td>25/18</td>
</tr>
<tr>
<td></td>
<td>87/81</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>60/58</td>
</tr>
<tr>
<td></td>
<td>84/76</td>
</tr>
<tr>
<td></td>
<td>16/11</td>
</tr>
<tr>
<td></td>
<td>88/89</td>
</tr>
<tr>
<td>Cefepime</td>
<td>70/65</td>
</tr>
<tr>
<td></td>
<td>87/78</td>
</tr>
<tr>
<td></td>
<td>27/20</td>
</tr>
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<td></td>
<td>93/91</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>68/63</td>
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<tr>
<td></td>
<td>77/68</td>
</tr>
<tr>
<td></td>
<td>12/10</td>
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<td></td>
<td>62/64</td>
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<tr>
<td>Meropenem</td>
<td>72/66</td>
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<td>99/99</td>
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<td></td>
<td>58/46</td>
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<td>100/99</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>76/71</td>
</tr>
<tr>
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<td>76/71</td>
</tr>
<tr>
<td></td>
<td>19/11</td>
</tr>
<tr>
<td></td>
<td>71/70</td>
</tr>
</tbody>
</table>

**Note.** HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia; Boldface indicate ≥5% decrease in susceptibility for VABP isolates relative to HABP isolates (SENTRY 2004-2008).
Dose Decision Support

Pharmacokinetics: Patient population matters

Double Whammy

Impact of increased clearance and MIC in VABP vs. HABP

\[ r^2 = 0.86 \]

Preclinical data: Courtesy of William A. Craig


Double Whammy

Impact of increased clearance and MIC in VABP vs. HABP

Preclinical data: Courtesy of William A. Craig
Dose Decision Support

Pressure test dosing regimens

An NDA that arrives to FDA on time but with empty boxcars is useless
### Risky Study Sequence
Without Time for Thought

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
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<tbody>
<tr>
<td>Q1</td>
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<tr>
<td>Q4</td>
<td>Q4</td>
<td>Q4</td>
<td>Q4</td>
<td>Q4</td>
</tr>
</tbody>
</table>

- **File CTA**
- **Phase 1 SAD**
- **Phase 1 MAD**
- **File IND**
- **14C-ADME**
- **BAL Study**
- **Phase 3 – Indication cUTI (N=1,000)**
- **Phase 3 – Pathogen Study (N=150)**

Accelerated clinical development timeline
Develop the drug you have and not the one you wish you had.
ACKNOWLEDGMENTS

Many Thanks to those that continue to inform my thinking!

DAVID ANDES, M.D.
*University of Wisconsin*

WILLIAM A. CRAIG, M.D.
*University of Wisconsin*

MICHAEL N. DUDLEY, PHARM.D.
*The Medicines Company*

GEORGE L. DRUSANO, M.D.
*University of Florida*

JAMES KAHN, M.D.
*JBK Strategic Consultations*

JUSTIN BADER, PHARM.D.
*Institute for Clinical Pharmacodynamics*

SUJATA M. BHAVNANI, PHARM.D., MS
*Institute for Clinical Pharmacodynamics*

ALAN FOREST, PHARM.D.
*Institute for Clinical Pharmacodynamics*

ELIZABETH LAKOTA, PHARM.D.
*Institute for Clinical Pharmacodynamics*

CHRISTOPHER M. RUBINO, PHARM.D.
*Institute for Clinical Pharmacodynamics*
Thank you for your attention.