

Poorly Soluble Drugs
Pharmaceutical Development Strategies and
Approaches for Pre Clinical Applications

AAPS BADG & CACO Joint Scientific Session

Moderator: Ram Nyshadham

January 20th 2010, 6-9 PM

AAPS BADG -CACO Joint Meeting, 1/20/2010 (6-9PM)

- Overall: 6-9 PM
- Registration, Net Working, and Vendor Show: 6-7 PM
- Dinner and Scientific Talks – 6-9 PM
 - Opening remarks by joint leaders & Major BD: 7-7.15 PM
 - Introduction & Premise: 7.15-7.20 PM
 - Speaker 1*: 7.20-7.50 PM
 - Speaker 2*: 7.50-8.20 PM
 - Speaker 3*: 8.20-8.50 PM
 - Open Q&A: 8.50-9 PM
- Event close out: 9 PM (by Joint Leaders)

*Includes time for 2-3 questions

Agenda for Scientific Session

- Introduction & Premise
 - Ram Nyshadham
- Use of Amorphous API in Pre clinical
 - Dr. Karthik Nagapudi, Sr Scientist, Amgen
- Theory and Practice for Development of Enabling Formulations for Pre Clinical Studies
 - Dr. Sreekanth Nadkarni, Sr. Director, Formulation Development, FibroGen
 - Developability Assessment and Early Development Strategies
 - Dr. Sesa Neravennan, VP Pharmaceutical Development, Allergan

Introduction & Premise

Ram Nyshadham

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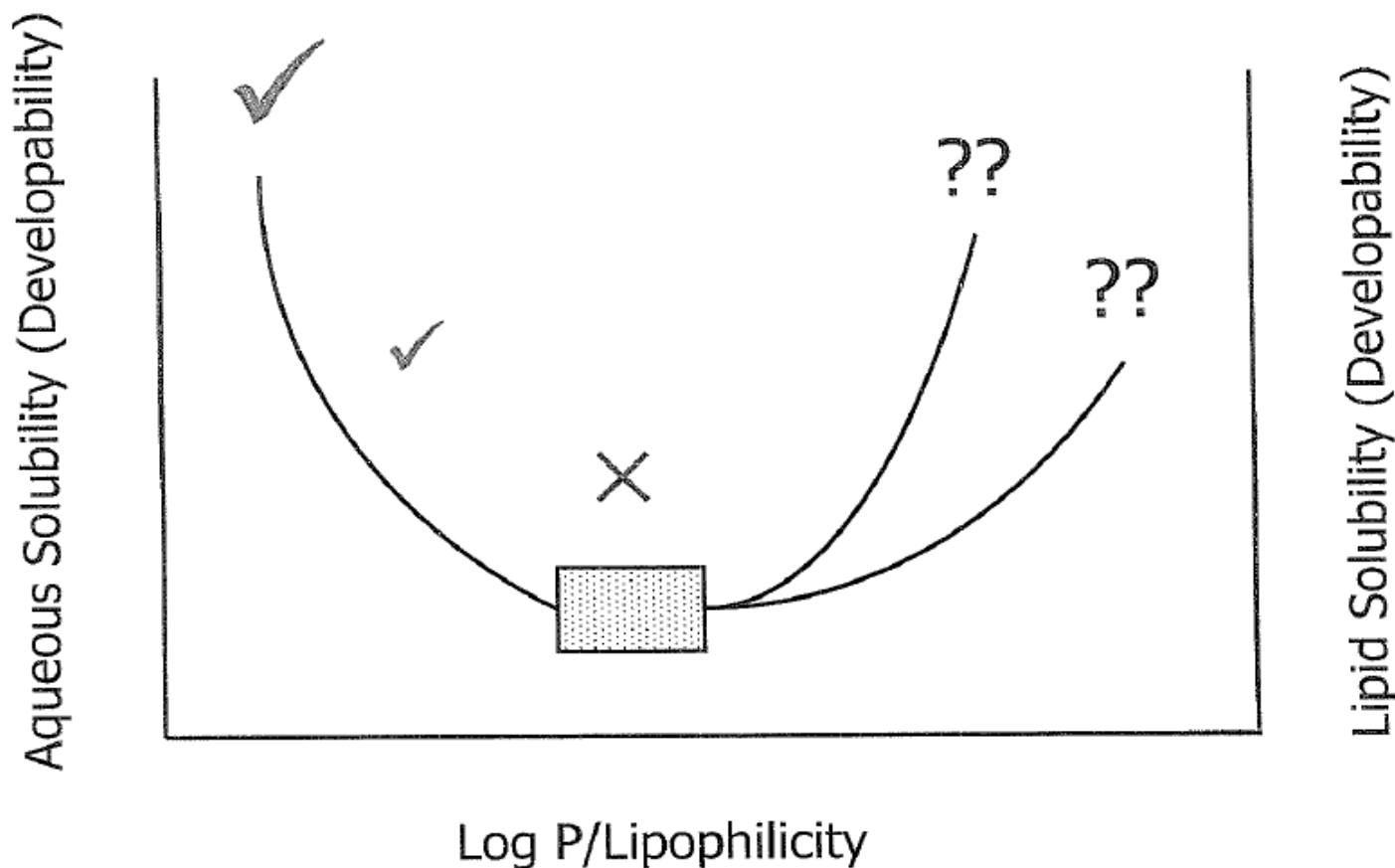
Issue is not just poor solubility
and look for “Magic” from PD ☺

Systems (I/O) approach

- Input Issues.....Impact beyond poor solubility
 - Log P is increasing
 - Higher Melting Point ($> 200^{\circ}\text{C}$)
 - Not soluble in ICH solvents either
 - Many more
- Out Put Impact:
 - Extremely large dose numbers
 - Programs can get stuck in pre clinical

Can More lipophilic be More Developable

Proff William Charman, AAPS Workshop on Lead Like candidates



Log P: 2 to ~ 3.5: Hard to formulate as lipid based systems

Log P > 4.5: Amenable to lipid based systems with some courage ☺

Log P: 3.5-4.5: Get Stuck !

Log P > 5: Lymphatic Transport

Dose Number: Function of Solubility & Dose

For 500 mg dose

Dose Number

100 $\mu\text{g/mL}$ (0.1 mg/mL)

20

10 $\mu\text{g/mL}$ (0.01 mg/mL)

200

1 $\mu\text{g/mL}$ (0.001 mg/mL)

2000

0.1 $\mu\text{g/mL}$ (0.0001 mg/mL)

20000

DN<20: Challenging but encouraging

DN>20: Extremely challenging; could be discouraging

So, how do we approach

No Magic 😊

Expert Opinion

1. Introduction
2. Animal species and

Preclinical formulations for discovery and toxicology: physicochemical challenges

Seshadri Neervannan
Amgen, Inc., Mail Stop 8-2-D, One Amgen Center Drive, Thousand Oaks, CA 91320, USA

Salt Selection: Biopharmaceutical Considerations

Sesha Neervannan, Ph.D.
Small Molecule Pharmaceuticals
Amgen Inc

Role of the development scientist in compound lead selection and optimization

Journal of Pharmaceutical Sciences

Volume 89, Issue 2, Date: February 2000, Pages: 145-154

Srini Venkatesh, Robert A. Lipper

Impact of solid state properties on developability assessment of drug candidates

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Estimating drug solubility in the gastrointestinal tract[☆]

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TABLE 2

Average changes in physical properties from lead to drug [12]

Property	Change from leads to drugs
MW	+69
ClogP	+0.43
# Rings	+1
HBAs	+1
Rotatable bonds	+2

www.elsevier.com/locate/ijjg

Commentary

Pharmaceutical evaluation of early development candidates "the 100 mg-approach"

Stefan Balbach^{*}, Christian Korn

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Received 12 August 2003; received in revised form 23 January 2004; accepted 27 January 2004

Intangible Success Factors

- Discovery teams should involve PD early on
- **Adequate & critical** characterization of candidates
- Developability assessment, by PD Group, prior to candidate nomination
- All formulations - key in vivo pharmacology, Tox, PK studies for nomination – be provided by PD scientists
- Rationalize approaches for pre clinical that can be distinct from FIH
- Carefully deploy “Enabling Formulations
- **PD scientists should do more to reach out to pre clinical functions**

Today's Scope

- Mostly Limited to Oral Delivery:
 - Poor solubility relevant to iv / ocular delivery too
- Pre clinical
 - but will make excursion to clinical
- Does not include
 - Pro drugs, Co crystals
 - Hot Melt Extrusion, Nano Systems, SCF, etc
 - And many more

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