Welcome to:

# Avoiding Drug Failures: Right First Time; Fast First Time

## Conducted by:
## The Crystal Panel

Joe Armstrong, Ph.D.
Executive VP
Global Head of R&D
TCG GreenChem, Inc.

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PharmaSolv Consulting, Inc.

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Owner, Triform Sciences

Eric Munson, Ph.D.
Professor
Purdue University

Chris Senanayake, Ph.D.
Chief Executive Officer
TCG GreenChem, Inc.

Greg Stephenson, Ph.D.
Senior Research Fellow
Crystal Pharmatech

## Moderator

Robert Wenslow, Ph.D.
Crystal Pharmatech
Head of US Operations

Crystal Pharmatech

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# Avoiding Drug Failures Right First Time; Fast First Time

Impact of API Form and Formulation

**Crystal Panel**

## Mission Statement：

*Vetting of API forms and formulations for First-in-Human studies is critical to maintain the integrity of downstream processes. Making best-in-class decisions utilizes a data-driven, multi-disciplinary approach based on institutional knowledge and comparative analysis. We rely on the key, basic, solid-state scientific principles of physical properties, solubility, stability, processability and isolation complexity needed to ensure the API phase and formulation are understood to a level of detail ensuring downstream processes are robust.*

# Panel Discussion

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- Milestone Driven Development
  - Silver –Phase I as fast as possible (Proof of Concept Model)
  - Gold –Phase I with a robust CMC package and Phase II ready
  - Platinum – Launch compound
- Mock Case Study
- Panel will discuss a faster, more efficient development with respect to form and formulation – highlighting necessary pieces for each milestone type

# API Form and Formulation Panel

## Paul Luner

**Senior Scientific Advisor (Crystal Pharmatech)**

- Ph.D. in Pharmaceutics, University of Michigan
- 30 years' experience spanning drug substance and drug product development.
- Expert in Solid State and Pharmaceutical Materials Characterization:
- Held group leader positions at Warner Lambert, Pfizer and Boehringer Ingelheim in the area of preformulation, formulation and solid-state sciences

## Sophie-Dorothée Clas

**Principal and Consultant, PharmaSolv Consulting, Inc.**

- Ph.D. in Polymer Chemistry, McGill University
- 23 years' experience in Preformulation and Discovery Pharmaceutics - Merck Frosst Canada, Merck & Co (West Point)
- Co-authored on 14 patents and 49 referred publications, and has contributed to more than 80 oral and poster presentations, 32 of which as invited speaker

## Joe Armstrong

**Executive Vice President, Global Head of Research and Development, TCG GreenChem, Inc.**

- Ph.D. in Synthetic Organic Chemistry, University of Colorado Boulder
- Executive Vice President, AstaTech, Inc., AstaGreen Chem., Inc. (2019)
- President, Pachamama LLC. (2018 - 2019)
- Executive Director, Process Chemistry, Merck & Co., Inc. (2011 - 2018)

# API Form and Formulation Panel

## Chris Senanayake

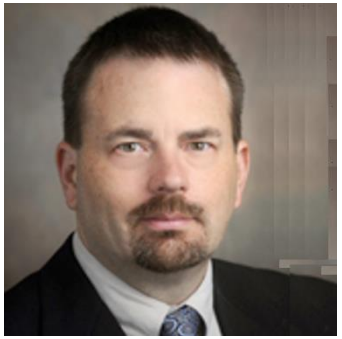
**Chief Executive Officer, TCG GreenChem, Inc.**

- Ph.D. in Synthetic Organic Chemistry, Wayne State University
- Chief Executive Officer, AstaTech (Chengdu) Biopharmaceutical Corp and AstaGreen Chem, Inc. (2018 - 2019)
- Vice President, Chemical Development, Boehringer Ingelheim Pharmaceutical (2002 - 2018)
- Executive Director, Sepracor Inc. (1996 - 2002)

## Dr. Greg Stephenson

**Senior Research Fellow (Crystal Pharmatech)**

- Ph.D. in Solid State Chemistry, Purdue University
- 30 years' experience in Eli Lilly and Company
- Expert in trouble shooting issues concerning crystallization, interfacing with drug discovery program teams, studying and selecting solid state forms for commercial development
- Awarded approximately 14 patents and 65 publications in the field of solid-state pharmaceutical chemistry of pharmaceuticals

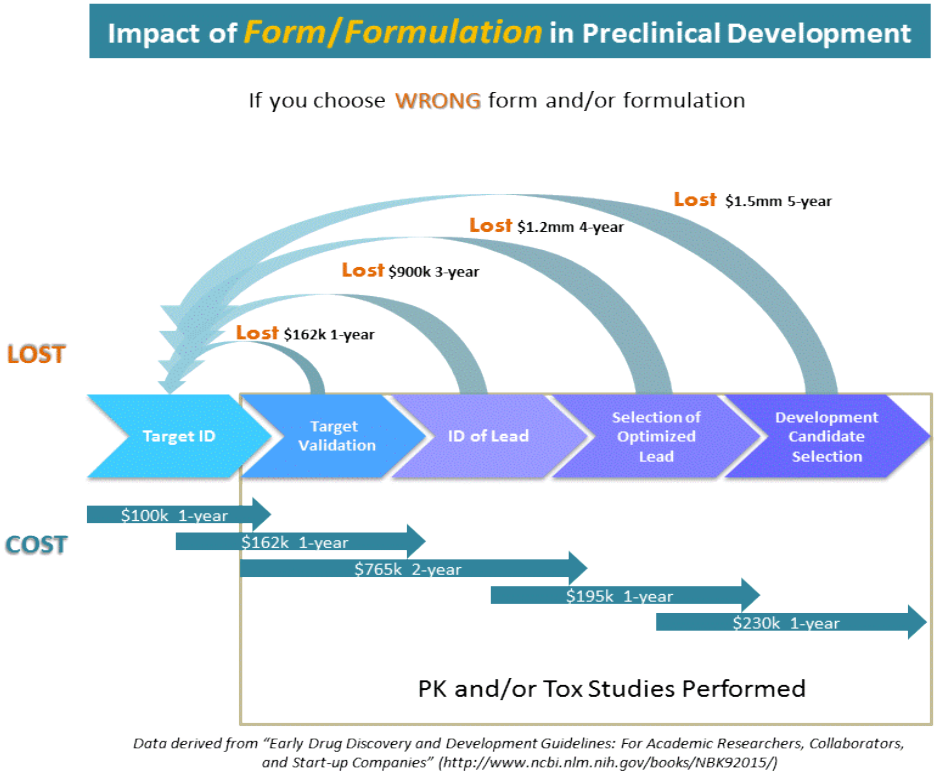


## Eric J. Munson

**Professor at Purdue University**

- Ph.D. - Texas A&M University
- Dane O. Kildsig Chair and Head of the Industrial and Physical Pharmacy Department at Purdue University
- Coinventor on three patents and has published more than 100 research, review, and book chapters

# Failures due to API Form and Formulation




https://drug-dev.com/drug-development-dont-overlook-key-preclinical-research/

# Molecules, Materials, Medicines

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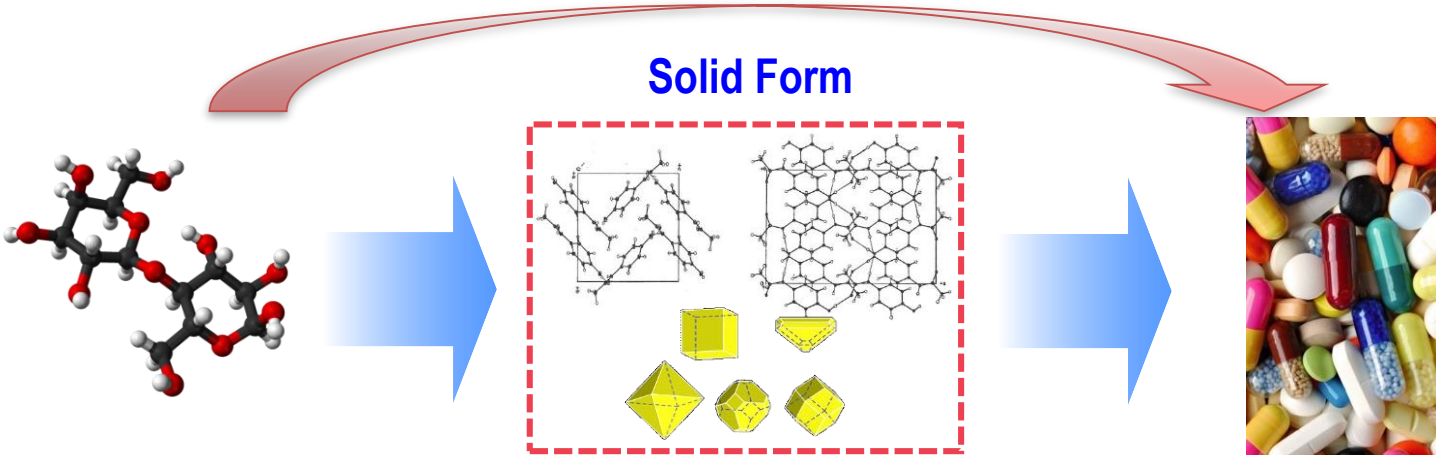
## Critical Role of API Form and Formulation




**Active Pharmaceutical Ingredient**

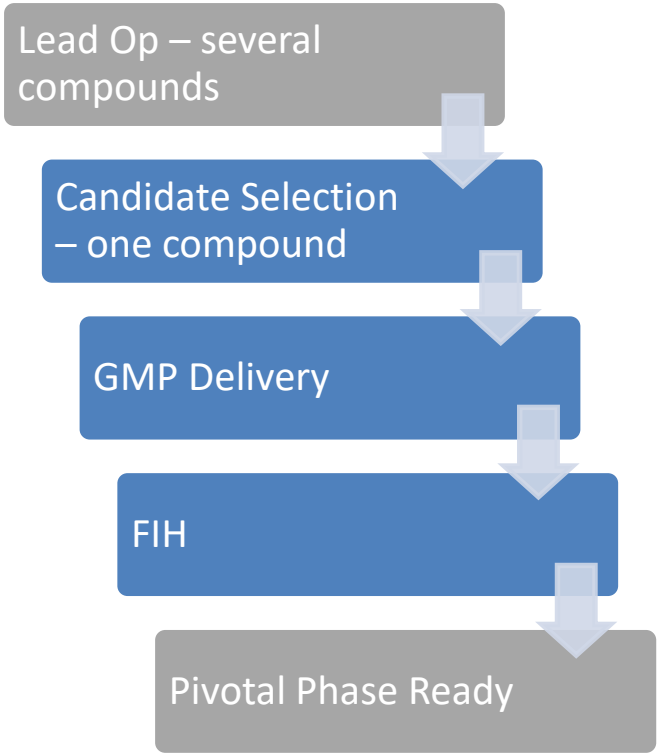
**API Crystals**

- *Chemical purity*
- *Structure (polymorph)*
- *PSD, SA, morphology, density, etc.*
- *Stability (chemical and/or physical)*
- *Hygroscopisity, color, caking, etc.*

**Drug Product**

- *Bioavailability*
- *Efficacy*
- *Safety*

# API Focus



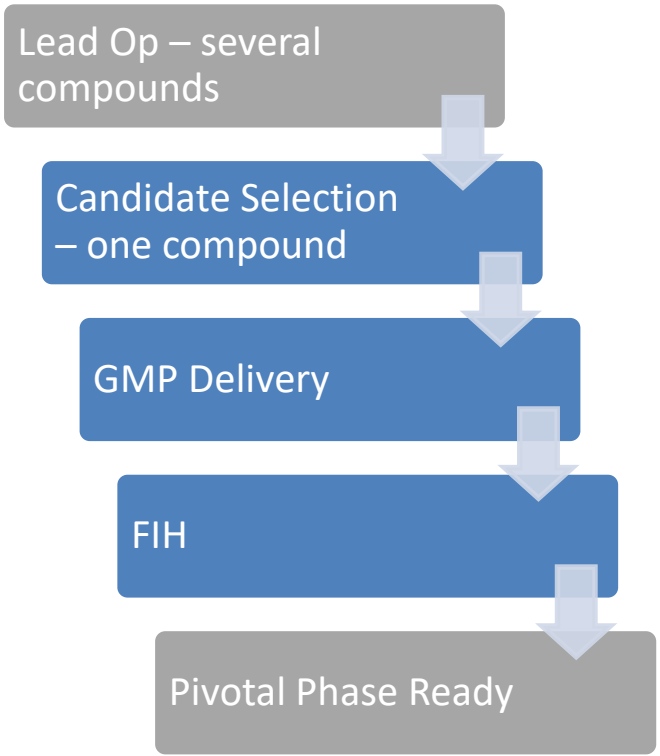

Fundamental Data - pKa, Log P, pH sol, biorelevant kinetic solubility (always checking phase)

Consistent Plasma Levels - Amorp vs. crystalline, morphology, melt, hygroscopicity, stable phase, salt or free

Salt Selection - Reproducible, isolatable, scalable, physical/chemical purity, physical/chem stability (process-induced phase transformations), non-hygroscopic (packaging, choice of excipients)

Regulatory - Meets target stability duration, structure elucidation (CMC)

# Formulation Focus




FIH Plans - Compounding, drug in capsule, food concerns, solution, suspension, DFC, Tablet

Fundamental Data - Dose number, MAD, solubility vs. pH, BCS, ADME, Efflux, Adsorption

Stability - Force Deg, stability indicating method, process induced phase changes, DP chem/phys stability

Regulatory - Meet ICH, disso and biorelevant targets, excipient sourcing

# Package Deliverables

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## SILVER
*POC Model*

Identification and characterization of API Form suitable for tox and FIH

Information to de-risk development of phase, chemical and physical stability information on the selected phase

Chemical and physical stability of the optimum formulation for oral dosing in preclinical species for a duration suitable for the dosing group

Understand phase risks with respect to TPP

## GOLD
*Phase II Ready*

API Form suitable for solid oral dosage formulation and transition to a manufacturable Ph II level.

Full vetting of API form. Full salt and polymorph selection.

Form control in API and drug product, understanding impact of PSD

Formulation – scalable at Ph II production ~ 10-30Kg batch. Support 1 yr shelf life.

Establish robustness of form relative to pre-requisites of TPP

Screen early for chemical stability issues to define formulation constraints

## PLATINUM
*Launch*

Fundamental data at lead op stage (pKa, Log P, Permeability, Dose number, BCS, PK studies to determine impact of form and PSD full forced deg with HPLC method development (impurity indicating)

Free form thermodynamic screening, single crystal

Salt selection for exposure and isolation, single crystal – several arm animal studies to confirm form and formulation

Understand all process induced phase changes

Excipient compatibility early

Crystallization development for form and PSD control

Formulation development – impact of form and particle attributes

Full IP Screening after Phase I

Full phase selection for all isolated intermediates

2nd gen visibility for efficiency

# Case Study – CP-9944

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***At candidate selection stage working towards GMP delivery***

## Target Product Profile

- NCE
- Chronic Treatment – non- oncology
- Oral Administration
- Solid Dosage Form
- FIH powder in capsule
- BID Dosing
- Food Effect Studies after POC
- Fassif 0.1mg/ml; SGF 6mg/ml (24 hours FB)
- 10mpk solution similar to HPMC suspension
  Cmax and AUC – dosed as free base

## Solid State

- MW = 400
- pKa = 9.2 (acidic), 3.3, 1.8
- Log P = 2
- Crystalline free base (MP 140 followed by decomp polymorph unknown)
- Crystalline tartrate salt (MP ~140 – no known polymorphs)

***Free base or salt***

***Conventional or non-conventional formulation***

# What is missing for Case Study

| What | Why | How |
|---|---|---|
| Permeability | BCS…. | CACO-2? A-B |
| Structure | pKa determination | |
| Log P | Lipophilicity | |
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| What | Why | How |
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# Immediate Actions

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| What | Priority | Package |
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# The Actual Case Study

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**API**

Jan 2015
4 compounds
FB and Tartrate chosen as leads for CP-9944

Aug 2015
CP-9944 Tartrate Chosen – no known polymorphs

Dec 2015
GMP delivery
Polymorph concerns with Tartrate – Co-Crystal

Feb 2016
Dispro concerns with tartrate during isolation


**Formulation**

Feb 2015
Strong pH solubility dependence; early PK at 10 mpk similar AUC and Cmax for solution and suspension dosed as tartrate

Sep 2015
Formulation for FIH powder in capsule

Mar 2016
H to H PK 10mpk
FB = 70% of tartrate

# References


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# Selecting the Right API Form and Formulation

## Webinar Series

***October 1, 2020 at 1:00-2:00 PM EST***

Speaker: Paul Luner, Ph.D., Senior Scientific Advisor, Crystal Pharmatech
Title: Tools and Strategies for De-risking Rapid Drug Substance and Drug Product Development

***November 5, 2020 at 1:00-2:00 PM EST***

Speaker: Eric Munson, Ph.D., Crystal Panel Member of Crystal Pharmatech
Title: Advancements in Analytical Tools for API and DP Characterization

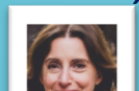
***December 3, 2020 at 1:00-2:00 PM EST***

Speaker: Greg Stephenson, Ph.D., Senior Research Fellow, Crystal Pharmatech
Title: Utility of Single Crystal in Form and Formulation Selection

***January 7, 2021 at 1:00-2:00 PM EST***

Speaker: Robert Wenslow, Ph.D., Co-founder and Head of US Operations, Crystal Pharmatech
Title: Solid Forms: The Good; The Bad; The Ugly

***March 4, 2021 at 1:00-2:00 PM EST***



Speaker: Sophie-Dorothee Clas, Ph.D., Crystal Panel Member of Crystal Pharmatech
Title: Formulation Implications