We will begin momentarily at 2pm ET

Recordings will be available to ACS members after two weeks

http://acswebinars.org

Contact ACS Webinars ® at acswebinars@acs.org

Have Questions?

“Why am I muted?”
Don’t worry. Everyone is muted except the presenter and host. Thank you and enjoy the show.

Type them into questions box!

Contact ACS Webinars ® at acswebinars@acs.org
Have you discovered the missing element?

www.acs.org/2joinACS
Find the many benefits of ACS membership!

Benefits of ACS Membership

Chemical & Engineering News (C&EN)
The preeminent weekly news source.

NEW! Free Access to ACS Presentations on Demand®
ACS Member only access to over 1,000 presentation recordings from recent ACS meetings and select events.

NEW! ACS Career Navigator
Your source for leadership development, professional education, career services, and much more.

www.acs.org/2joinACS
How has ACS Webinars® benefited you?

“I have learned a lot of what I am interested in during the Drug Discovery Series. For example, I have obtained the new information about the drug discovery process from both academics and industries.”

Fan of the Week

Zuping Xia, Ph.D.
Research Associate Professor, and Director of NMR Core, College of Pharmacy, Washington State University

Be a featured fan on an upcoming webinar! Write to us @ acswinaraacs.org

ACS Webinars®

facebook.com/acswinaraacs
@acswinaraacs
youtube.com/acswinaraacs

Stay connected...

Email us!
acswinaraacs.org
Hungry for a brain snack?

“ACS Webinets™ are 2 minute segments that bring you valuable insight from some of our most popular full length ACS Webinars®.”

See all the ACS Webinets at youtube.com/acswebinars

Beginning in 2014 all recordings of ACS Webinars will be available to current ACS members two weeks after the Live broadcast date.

Live weekly ACS Webinars will continue to be available to the general public.

Contact ACS Webinars® at acswebinars@acs.org
Upcoming ACS Webinars®
www.acs.org/acswebinars

Thursday, August 7, 2014
“How to Write Abstracts that Capture Your Audience”

Celia Elliott, University of Illinois at Urbana-Champaign
Patricia Blum, University of Illinois at Urbana-Champaign

Thursday, August 21, 2014
“Forecasting Chemistry: Predicting Tomorrow’s Cutting Edge Science, Today”

Dr. Charles Twardy, SciCast Project Principal and Professor at George Mason University

Contact ACS Webinars ® at acswinbins@acs.org

Did you miss the past recordings in the Drug Discovery Series?

Next in the Drug Discovery Series!

“Pharmacoeconomics and IP Strategies in Drug Development”

Thursday, September 25, 2014

The Role of Chemistry in Clinical Trials:
The Big Expense & Lessons Learned

Dr. Graham Johnson
President, NuPharmAdvise LLC

Dr. John Morrison
Senior Research Investigator,
Bristol-Myers Squibb

Dr. Jay Sisco
Founder, JM Sisco Pharma Consulting LLC
Past-President, AAPS

Recordings will be available to ACS members after two weeks

www.acswebinars.org

Contact acswbinars@acs.org for a copy of today’s slides
The Role of Chemistry in Clinical Trials

An ACS Webinar Presented by:
Dr. Graham Johnson – NuPharmAdvise, LLC
Dr. John M. “Jay” Sisco – JM Sisco Pharma Consulting, LLC
Moderated by Dr. John Morrison – Bristol-Myers Squibb

Our Objective

- Create awareness and understanding of what happens between lead candidate selection and NDA submission that translates into better drug design and lead candidate selection

- A small investment up front can translate into huge savings later on
Clinical Trials

- The sole objective of clinical trials are to define the safety, tolerability/side effects, effectiveness and dose of a new drug and create the knowledge base on which the FDA can approve its use and sale.

- The “chemistry” of a new drug makes up a critical part of this knowledge base.
Drug Product Development

- Facilitation of repeated safe delivery of the correct quantity of active substance at the correct rate to the desired body compartment

- Guaranteed until the expiry date

★★ Every Time ★★

Chemistry, Manufacturing & Controls

- **Chemical R&D:** reliable, reproducible, scalable synthetic API process

- **Pharmaceutical R&D:** physicochemical properties of the API, drug product phase appropriate formulations – stable and deliver the correct dose

- **Analytical R&D:** analytical methodologies - release testing and stability evaluation of API and drug product.

- **Quality:** ensures compliance - regulations that govern the manufacture, analysis, packaging, labeling and shipping of API and drug product.

- **Reg.CMC:** author CMC section of submissions, interact with regulatory authorities on matters concerning CMC

- **Supply Chain:** manufacture, package, label and ship clinical trial material
What is the *Chemistry* of a Drug

- **To the FDA**
  - A stable *active pharmaceutical ingredient* (API) that can be made in completely defined and controlled process that produces a product of consistent purity, chirality, stability and physical form

- **To the Company**
  - A compound that can be consistently made by a process that provides the greatest profit margin or lowest “Cost of Goods”

Bridging the Divide

- **Medicinal chemistry** - the interface of organic chemistry with biological systems. The objective is the discovery of new drugs through the generation of structural diversity and understanding its relationship to biological activity

- **Process chemistry** - the interface of organic chemistry with business. The objective is the manufacture of a specific molecule and a defined form with a high degree of quality both cost effectively and with low environmental impact.
Different Strokes for Different Folks

• To the Medicinal Chemist
  – *The product is the driver!* – how it is made and what goes on in the flask is of less importance

• To the Process Chemist
  – *The process is the driver* – understanding and controlling every facet of what goes on in the flask is critical

• To the Formulation Chemist
  – *The properties are the driver* – creating an active and commercially viable formulation depends on them

Operating in Different Worlds

Discovery Chemistry
  – All reaction types, reagents and solvents are on the table – *if you can buy it you can use it!*
  – Temperatures from -110 to +300 – *no problem!*
  – Reaction concentration – *what is that?*
  – Specialized equipment – high pressure hydrogenation, microwave reactors – *absolutely we’ve got that!*
  – Purification – *HPLC does the trick every time!*
  – Safety – *if I am not working with diazomethane or HF why do I need to worry?*
Operating in Different Worlds

**Process Chemistry**
- Safety is a primary driver
- Stability, toxicity, disposal and allowed residues limit choices
- Temperatures outside -20°C to +120°C are a challenge
- Most chemistry is bimolecular – concentrated reactions work better and save on many levels
- Chromatography is expensive - crystalline solids are the workhorse of isolation and purification
- Controlling crystallization is essential
- Specialized equipment offer options to solve chemical problems – **flow reactors**

**Continuous Flow Reactors – The Concept**

![Diagram of continuous flow reactor system](image)
Continuous Flow Reactors - Expanding What is Possible

- Flow reactors permit smaller reaction vessels – unlimited scalability
- Chemistry can be run 24hrs a day
- In line continuous analysis of conditions and product
- Safety is ensured by carefully controlled reactor cross section and flow rates
- Fast and efficient mixing for rapid reactions
- Highly exothermic reactions become manageable
- Microwave heating, cooling, photolysis, increased pressure are all possible
- **Quality, reproducibility and safety are ensured**

**Case Study - Naproxcinod**

![Chemical Structure](image)

- Collaboration between Nicox, DSM and Corning Glass
- Concern for exothermic breakdown of the product
- Key intermediate nitrated using 65% nitric acid
- Reaction flow continues into quench and neutralization
Scaling by Parallel Processing

Multiplexed product delivery = 14kg/hr

1mm reaction channels

DSM produced 25 metric tons of API under cGMP conditions!

Crystal Form – Polymorphism

“The ability of a solid material to exist in two or more crystalline phases with different arrangements or conformations in the crystal lattice.”

Greek: “poly” = many
“morph” = forms

Polymorph → Crystalline
Amorphous → Non-crystalline
Pseudopolymorphs → Hydrate/Solvate
Polymorphism

Same chemical structure
Molecules arranged differently in the unit cell

Different Physical & Chemical Properties

Polymorphism

Effects physicochemical and pharmaceutical properties of the API

Packing: Density
Thermodynamic: Solubility, Free Energy, Melting Point
Spectroscopic: Vibrational Transitions
Kinetic: Reactivity, Dissolution, Stability
Mechanical: Hardness, Tensile Strength
Pharmaceutical: Flowability, Compatibility, Compressability

API & DP Manufacturing & Bioavailability

- Quality
- Safety
- Efficacy
Biopharmaceutics Classification System (BCS)

Volume Required to Dissolve the Highest Dose (mL)

Permeability (1x10^-6 cm/s)

Class 1
High Solubility
High Permeability

Class 2
Low Solubility
High Permeability

Class 3
High Solubility
Low Permeability

Class 4
Low Solubility
Low Permeability

Case Study
Effect of Polymorphism on the Manufacturing Process for the Drug Product

Lamivudine (3TC): GSK
Drug Product Processing - Flow

Lamivudine (3TC) – “Pseudopolymorphs”

Class: nRTI
Treatment: HIV 1&2
Hep B

3TC – Form 1

<table>
<thead>
<tr>
<th>Habit:</th>
<th>Needles</th>
<th>Crystallization Solv':</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting Point:</td>
<td>135ºC</td>
<td>Sol’y Stable Form:</td>
<td>Water &amp; MeOH</td>
</tr>
<tr>
<td>Solvate:</td>
<td>0.2 Hydrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystal Class:</td>
<td>Orthorhombic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z:</td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note Scale
**3TC – Form 2**

<table>
<thead>
<tr>
<th>Habit</th>
<th>bipyrimids</th>
<th>Crystallization Solv't:</th>
<th>IMS &amp; iso-PrOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting Point</td>
<td>178°C</td>
<td>Sol'y Stable Form:</td>
<td>EtOH, n-PrOH,</td>
</tr>
<tr>
<td>Solvate</td>
<td>non-solvated</td>
<td></td>
<td>iso-PrOH, n-BuOH</td>
</tr>
<tr>
<td>Crystal Class</td>
<td>tetragonal</td>
<td></td>
<td>sec-BuOH, EtOAc</td>
</tr>
<tr>
<td>Z</td>
<td>8</td>
<td></td>
<td>ACN, Acetone</td>
</tr>
</tbody>
</table>

**Case Study**

**Polymorphism Effect on Bioavailability**

Chloramphenicol Palmitate
Chloramphenicol Palmitate

Prodrug of chloramphenicol

3 Polymorphs:  
A (stable)  
B (metastable)  
C (unstable)

Bioavailability of Polymorphic Forms

Comparison of mean blood serum levels of chloramphenicol after dosing suspensions containing varying ratios of the A and B polymorphs of the prodrug chloramphenicol palmitate (expressed as %B polymorph).
Case Study

Polymorphism Effect on Solubility

Ritonavir: Abbott

Ritonavir

Protease Inhibitor: HIV1&2
Marketed by Abbott: 1996

- Not bioavailable from the solid state
- Solution and capsule formulations:
  - Soft-gel capsules: ritonavir in EtOH/water
- Single crystal form identified during development
- 240 lots of capsules manufactured
- No stability issues
The Rest of the Story

• Mid-1998 batches of capsules failed dissolution
• Capsules analyzed by microscopy and XRD
  – New polymorph – Form II
  – Greatly reduced solubility
• Once seed crystals appeared - new polymorph everywhere
• Hydro-alcoholic capsule formulation:
  – Not saturated with respect to Form 1
  – 400% supersaturated with respect to Form II
• Formulation could no longer be manufactured
• Seriously threatened the supply of a life saving drug

Ritonavir Polymorphs

Form I Form II
Case Study
Insoluble and Permeability Limited Absorption

Torcetrapib: Pfizer

Torcetrapib
Cholesteryl-ester transfer protein inhibitor (CETP-inhibitor)

Combination product: torcetrapib & atorvastatin

"Second coming of Lipitor"

- Poorly solubility
- Highly lipophilic Log P ~7.5
- Absorption - highly variable
- Significant food effect
Torcetrapib/Atorvastatin Combination

- Development started in 1990
  - **Torcetrapib SDD:**
    torcetrapib: hydroxypropyl methylcellulose acetate-succinate (1:3 w/w)
    spray-dried from solution in acetone
    stable amorphous spray-dried dispersion
  - **Torcetrapib SDD – CR:**
    torcetrapib SDD in an osmotic-pump controlled-release tablet
  - **Torcetrapib Drug Product:**
    torcetrapib SDD – CR coated with IR layer of atorvastatin

Torcetripib Clinical Program

- Clinical trials started in 1999
- December, 2006 - Independent Data Safety Monitoring Board
  - Recommended termination of a 15,000 patient Phase 3 clinical study
  - “Imbalance of mortality and cardiovascular events”
    patients taking torcetripib/atorvastatin experienced excess deaths compared to those taking Lipitor alone.
- Early in 2007 development stopped on the “Prized Asset”
The Result:
One of Pharma’s Biggest Flops

**GOOD:** Developed a new area of formulation science:

“Spray-Dried Dispersions”

**BAD:** Took 9 years to get into the clinic with the SDD formulation

**BAD:** Invested heavily - commercial manufacturing plant for API and SDD in Ireland

**BAD:** Very late Phase 3 failure

**BAD:** Estimated spend to failure > $800 million

**BAD:** Two weeks after failure announced, 10,000 jobs cut

---

Case Study

**Time to Market:**

Amorphous vs Crystalline API

Atorvastatin Calcium: Parke-Davis/Pfizer
Time to Market

“For every day a drug is delayed coming to market, a million dollars of revenue may be lost.”

“How many life-hours are lost for every day a drug is delayed coming to market?”

Atorvastatin Calcium – Lipitor

- Initial Development:
  - amorphous atorvastatin calcium Form B (later Form 23)
- No crystalline forms were known to exist
- Amorphous atorvastatin calcium
  - intrinsically unstable
  - can be stabilized through various additives to the formulation
The Rest of the Story

- Crystallized: trihydrate form - during late stage clinical trials

- Tablets were reformulated using crystalline API

- Extensive bioequivalence testing conducted:
  - Crystalline tablets – slower rate of absorption
  - However, the extent of absorption was the same

- FDA reviewed the clinical data relating to the two forms
  - Concluded that approval of the crystalline tablets was appropriate

The Moral of the Story

<table>
<thead>
<tr>
<th>Lipitor Peak Yearly Sales (2006):</th>
<th>$13.7 billion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 Year Delay to Market</td>
<td></td>
</tr>
<tr>
<td>Lost Revenue ~ $20.6 billion</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>~ $37.6 million/day</td>
<td></td>
</tr>
<tr>
<td>Number of life-hours lost:</td>
<td></td>
</tr>
<tr>
<td>? Indeterminate ?</td>
<td></td>
</tr>
</tbody>
</table>

Today: at least 47 known polymorphs various amorphous forms
Final Words

Safe  Pure  Effective

Every Time

Quality

Further Reading
Flow Reactors

Chemica Oggi/Chemistry Today 2011, 29, (3), 47-49
Chemica Oggi/Chemistry Today 2012, 30, (4), 42-44
Chemica Oggi/Chemistry Today 2012, 30, (4), 51-54
Chemica Oggi/Chemistry Today 2009, 27, (1), 26-29
C&E News 2009, 87, (11), 17-19
C&E News 2014, 92, (21), 13-21
Organic Process Research and Development 2011, 15, 1477-1453
Organic Process Research and Development 2012, 16, 1069-1081
Further Reading
Crystalline & Amorphous Solids


Upcoming ACS Webinars®
www.acs.org/acswebinars

Thursday, August 7, 2014
“How to Write Abstracts that Capture Your Audience”

Celia Elliott, University of Illinois at Urbana-Champaign
Patricia Blum, University of Illinois at Urbana-Champaign

Thursday, August 21, 2014
“Forecasting Chemistry: Predicting Tomorrow’s Cutting Edge Science, Today”

Dr. Charles Twardy, SciCast Project Principal and Professor at George Mason University

Contact ACS Webinars ® at acswebinars@acs.org

The Role of Chemistry in Clinical Trials:
The Big Expense & Lessons Learned

Dr. Graham Johnson
President, NuPharmAdvisors LLC

Dr. Jay Sisco
Founder, JM Sisco Pharma Consulting LLC
Past President, AAPS

Dr. John Morrison
Senior Research Investigator, Bristol-Myers Squibb

Recordings will be available to ACS members after two weeks
www.acswebinars.org

Contact acswebinars@acs.org for a copy of today’s slides
Next in the Drug Discovery Series!

“Pharmacoeconomics and IP Strategies in Drug Development”

Thursday, September 25, 2014

How has ACS Webinars® benefited you?

“I have learned a lot of what I am interested in during the Drug Discovery Series. For example, I have obtained the new information about the drug discovery process from both academics and industries.”

Fan of the Week

Zuping Xia, Ph.D.
Research Associate Professor, and Director of NMR Core, College of Pharmacy, Washington State University

Be a featured fan on an upcoming webinar! Write to us @ acswininars@acs.org
Benefits of ACS Membership

Chemical & Engineering News (C&EN)
The preeminent weekly news source.

NEW! Free Access to ACS Presentations on Demand®
ACS Member only access to over 1,000 presentation recordings from recent ACS meetings and select events.

NEW! ACS Career Navigator
Your source for leadership development, professional education, career services, and much more.

www.acs.org/2joinACS
ACS Webinars® does not endorse any products or services. The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the American Chemical Society.

Contact ACS Webinars® at acswebinars@acs.org

Upcoming ACS Webinars®
www.acs.org/acswebinars

Thursday, August 7, 2014
“How to Write Abstracts that Capture Your Audience”

Celia Elliott, University of Illinois at Urbana-Champaign
Patricia Blum, University of Illinois at Urbana-Champaign

Thursday, August 21, 2014
“Forecasting Chemistry: Predicting Tomorrow’s Cutting Edge Science, Today”

Dr. Charles Twardy, SciCast Project Principal and Professor at George Mason University

Contact ACS Webinars® at acswebinars@acs.org