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Challenges in Early Phase API Scale Up

NCI Drug Development Workshop Session IV

August 20, 2021

Wrapping Your Head Around the Challenges of Scale Up

- Prepare a prepackaged macaroni and cheese dinner for two (med-chem)
  - One box; instructions on box are adequate
  - Equipment readily available in your kitchen

- Prepare a prepackaged macaroni and cheese dinner for ten (PK studies)
  - Five boxes; still doable.

- Prepare a prepackaged macaroni and cheese dinner for two-thousand (Pre-clinical/clinical)
  - One thousand boxes!
  - We're going to need a bigger kitchen!

Key Elements of a Process Ready to Scale

- Safe
- Robust
- Inexpensive
- High Yielding

Early Process Development may involve development of a “fit for purpose” or “phase appropriate” process and/or development of a completely new synthetic route.

Safety: API Hazard Assessments

APIs are getting to lower and lower exposure bands (ng/m^3) – need to protect our workers. Intermediates need similar assessments.

Types of data needed:

- Toxicology or dosing data (often little to none available for first scale up)
- Therapeutic target/mode of action
- Structural analogy with known substances
- Occupational exposure level (OEL) banding/conservative default

Safety: Process Assessments

- Basic thermal hazard assessments should be performed on materials and steps involved in a process before scale up.

- Types of data needed:
  - DSC/ARC/TSU/RC1 for thermal decomposition and energetics
  - Dust explosivity (combustible dusts), detonative shock/impact (BAM “hammer” tests)
  - OEL banding
  - Electrostatic dissipation

Safety: PGI/Toxicity Assessments

API generally is fit into OEL band, but impurities now get heightened scrutiny

- Based on dosage of the API and a TTC risk assessment
- Genotoxicity assessments go from theoretical (DEREK/SARAH) to animal data models (Mouse micronucleus and Ames). Lots of companies now exist to do these assessments.
- Burden on analytical technology to keep up with the acceptable threshold levels (ppm to ppb).
- Changes to synthetic strategy frequently are made to compensate for these impurities.
- Beware use of alcoholic solvents with alkyl or aryl tosylates (or mesylates etc.) and with hydrohalic acids (e.g. Ethanol/conc. HCl).
- Even volatile PGIs (e.g. MeI) can become entrained in an API

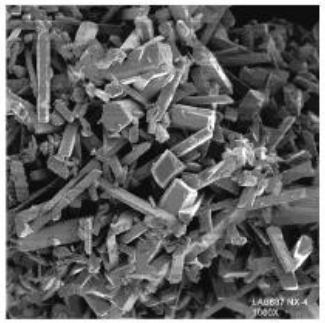
Safety: PGI/Toxicity Assessments

- Solvents are in this category, residual levels in APIs are governed by ICH Q3c
- ICH Class 1 (e.g. benzene, CCl_4) are almost impossible to use.
- Many common solvents have stringent, low residual limits
  - DCM 600 ppm
  - Aectonitrile 410 ppm
  - 1, 4-Dioxane 380 ppm
  - DME 100 ppm
  - THF 720 ppm
  - Pyridine 200 ppm

- New solvents are being developed. As these gain toxicology data and become economical, they are adopted.
  - Tamisolv- (N-butyl pyrrolidone)
  - Cyclopentyl methyl ether
  - 2-Methyl-THF
  - 4-Methyl-Tetrahydropyran

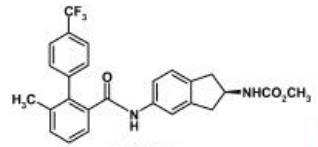
Robustness: Polymorphic Control

- Polymorphism stories have been known for many years, but this is still a major source of manufacturing challenge!
- Commitment to test for this during development- often a risk decision.
- There are many companies that will do this work
  - Typically takes 4-8 weeks for polymorph screen and initial characterization.
  - Can be performed in parallel with process development of early steps.
- Seeding is the norm, not the exception, for controlling morphology
- QbD work typically maps the metastable zones to predict the crystallization behavior based on temperature and saturation solubility
- Control of impurity purging.
- Consistency of drying times.
- Control for intermediates is just as important



Form B

Was initial material



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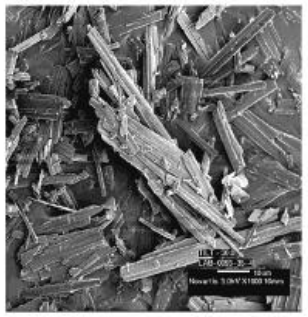
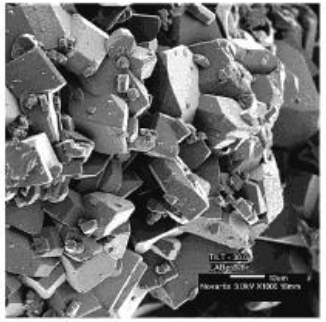


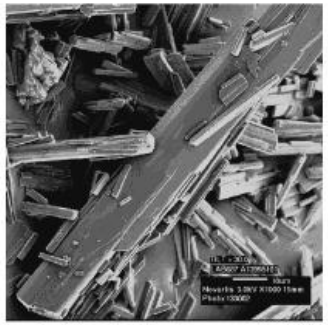
Form A

Next, discovered new polymorph: "Form A". Embarked on polymorph investigation...



Form C

...and discovered "Form C"; now Form B cannot be made in laboratories

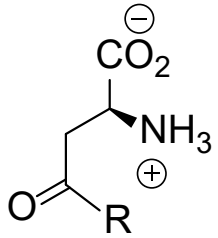


Form D

Selected and scaled up "Form C" in pilot plant, where "Form D" was discovered and began to predominate. Aiiieeeee!

Pictures and structure from Prashad et al., Org. Process Res. Dev. 2010, ASAP.
DOI: 10.1021/op100115u

Polymorphic Control Intermediate Case Study

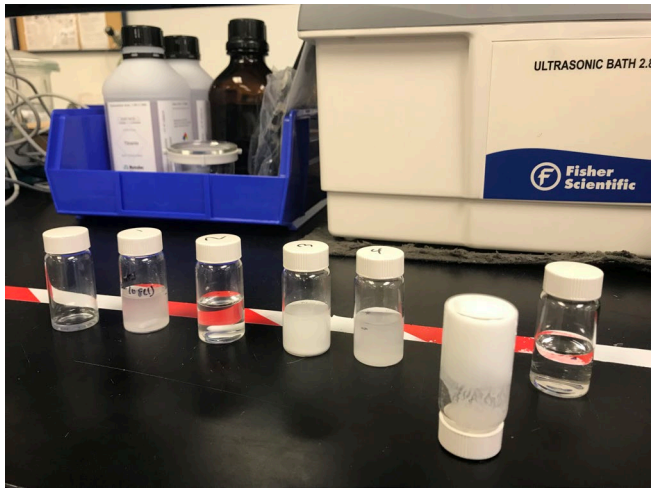


Zwitterionic API with an aqueous based formulation. The program skipped an upfront polymorph study as initial med chem scale batches afforded a highly water soluble crystalline form.

- Initial process development led to API isolation by lyophilization which afforded amorphous form.
- During processing of batch 11, a new water insoluble polymorph precipitated
- Within hours new polymorph also precipitated from batch 12.
- Solubility tests performed with retain samples from previous batches proved the new polymorph was proliferating.

Cost: *Polymorph study identified soluble salt form; process, formulation, and analytical test methods all had to be redeveloped.*

Ultimate cost: 14-16 months of clinical hold!



Polymorphic Control Intermediate Case Study

Tech transfer documents described isolation of a soluble bis-acid salt.

Process group observed isolation of insoluble mono-acid salt.

Highlights the importance of familiarization/demo batch during tech transfer.

- Operation was performed rapidly at previous scale (not stressed) and resulted in isolation of meta-stable bis acid salt.
- When operation was stressed in anticipation of longer times at scale, the more stable mono-acid salt was isolated.

Robustness: Considerations for Preclinical and First GMP Batch

- Initial process safety considerations
- Replace hazardous reagents/chemistries
- Remove chromatography and implement crystallization if possible
- Minimize volumes of reactions and workups
- Rudimentary stability at various points of the process.
- Early understanding of impurities and how to purge them
- Identify suitable GMP starting material(s)

*In the end due to time pressure, it may be necessary to practice almost any chemistry/technology required to get the first GMP batch. (e.g high catalyst loading, chromatography, protections/deprotections)

Robustness: The Drawbacks of Chromatography

The Good

- Provides a quick, convenient method for purification early in a programs lifecycle.
- Provides material of high purity (double edged sword!).

The Bad

- Time and labor intensive.
- Expensive materials (especially for reverse phase).
- Solvent intensive/generates significant waste.
- Throughput is limited, especially as material needs increase.
- Early batches can be 'too pure,' especially toxicology batches.
- Impurity profiles obtained by chromatography can be difficult to duplicate by non-chromatographic methods.
- May require toxicological bridging studies of later batches.

Robustness: The Importance of Stressing Your Process

- Operations on scale up (heating, cooling, distillation) invariably take longer than on small scale.
- Extended heating (including product drying), cool downs, distillation and hold times can result in impurity growth not seen on small scale, where operations can be executed fairly rapidly.
- Determination of suitable 'hold points' is often necessary.
- Depending on solvent a full 200-L reactor can take 3–4 hours to heat to 100 °C and the same time to cool.
- Many solvents are inherently reactive (e.g. dichloromethane, acetone, alcohols) and can interact with starting materials, intermediates, or products.
- Stress testing, extended heating, cool down periods are critical to ensure robustness and avoid unexpected low level impurities.

Robustness: The Importance of Stressing Your Process

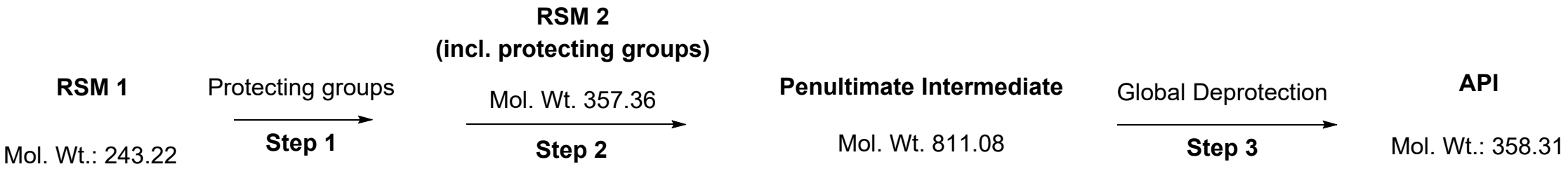
- Case Study 1: Extraction with dichloromethane
  - Phase splits for a compound which was being extracted with DCM took significantly longer on scale up. The product, a tertiary amine, reacted over time with DCM to generate ~1% of a quaternary salt impurity.

- Case Study 2: Sensitivity to silica gel
  - A natural product was purified on small scale by Biotage Flash chromatography. Elution time was 5–10 minutes on small scale, but ~ 4 hours on scale up. Significant degradation of material was observed and it was subsequently shown that this degradation occurred on extended exposure to silica gel.

Robustness: The Importance of Throughput Optimization

- Volume efficiency is measured as the number of unit volumes required per unit mass
  - 1 kg in 10 L = 10 volumes (desirable)
  - 1 kg in 100 L = 100 volumes (undesirable)
- Volume efficiency determines how much API can be produced in a single batch out of an equipment train.
- Good volume efficiency leads to increased throughput, faster throughput, less waste and thus lowers out cost of production.
- Poor volume efficiency results in low throughput, higher production costs and higher waste disposal.

Robustness: The Importance of Throughput Optimization



3.5 kg

11.7 kg

5 kg

- Unit volumes are normally based on the input mass of starting material for each individual step.
- Abundant use of protecting groups more than triples the mass of the penultimate creating a bottleneck at the final step.
- Need to move final step to a much larger equipment train or perform the last step in multiple batches.

Conclusions

- Recognize that work needs to be done on the process development, analytical, and safety front to make the success of your first scaleup batch a reality.
- Robustness is the target, but it's ok make some concessions in a "fit for purpose" process to get your phase I material. Improvements can always be made to the process for phase II/III supply.
- Although, some concessions can be made in terms of efficiency for your first scale up batch, safety is an absolute must.
- Stressing operations and determination of suitable 'hold points' is necessary.
- A polymorph study at the start of development may prevent a lot of heartache in the future