Development and Scale up in API Manufacture (Part 1)

Tuesday 22nd September 2009

Dr. Claire Mc Donnell, D.I.T.
Contents

- Terminology
- Development Stages
  - Chemical Development
  - Process Development and Support
- Costing
- Scale-up
- Case Study – Process Development for Labetalol Manufacture
- Summary
- Bibliography
Background

“drug” – a compound that interacts with a biological molecule, triggering a physiological effect.

Drugs (active pharmaceutical ingredients) can be classified into 4 groups depending on their origin;
1) Natural products
2) Fermentation products
3) Semisynthetics – substances produced by partial synthesis
4) Completely synthetic products
Will cover synthetic aspects of pharmaceutical production processes.
Background

- Average cost of developing a drug was $500 million in 1999 and takes 12-25 years usually.

- The chances of a candidate drug that is identified becoming approved is approximately 1 in 10,000. (For every 10,000 trial compounds, 20 reach trials on animals, 10 reach clinical trials on humans and 1 gets FDA approval)

- Discovery stage (research labs) involves preparation of potential drug compound on 10 mg to 10 g scale. Toxicology tests are carried out on this material. If these are successful, greater quantities of the compound will be required for clinical trials.

- At this stage, development work begins.
  - Immediate goal – to produce clinical trial material.
  - Longer term goal – to develop a commercially viable scaled-up validated process.
Terminology

- **Development**— covers all work between research and production (e.g. analytical, chemical, formulation) and **continues** when production begins.

- **Scale-up** – process of going from laboratory preparation to whatever scale of manufacture is required to satisfy the market demand (usually 1,000 to 50,000 L range)

- **Technology Transfer**
  - Transfer between manufacturing sites
  - Transfer within a manufacturing site
  (Partnerships for collaborative R&D)
What is Development?

- Broad range - between research and production - and overlaps with both
- In API (Active Pharmaceutical Ingredient) manufacture, begins when active substance is identified and activity demonstrated and more active substance is required.
- Once a process that works on plant scale is produced and is validated, development work still continues to improve cost, efficiency, quality and environmental impact and to deal with changing circumstances (vendors, equipment, new regulations (FDA 21 CFR part 11, Risk-Based Approach etc))
Development Stages

1) Chemical Development

Begins when activity of potential API is demonstrated and more active substance is required (for clinical trials).

Process research;
- New synthetic routes (literature survey)
- Some initial optimisation
- Yield improvements
- Possibly scale-up to large lab equipment / kilo lab (up to about 20 L)
2) Process Development
- Optimisation (change conditions and parameters)
- Minor change of route / intermediate
- Cheaper / more efficient reagents (new to market)
- Environmentally-friendly reagents and effluent considerations
- Yield / concentration improvement
- Statistical methods
  (e.g. Experimental Design; want maximum amount of unbiased information about factors affecting a process from as few observations as possible. Caution - “Facts are stubborn things. Statistics are more pliable”)
Development Stages cont’d

- **Process Development cont’d**
  - SCALE-UP (Kilo Lab, Pilot plant trials)
  - Transfer to Manufacturing

Parallel synthesis reactor block
- for optimisation of conditions
Development Stages cont’d

3) Process Support

- Further optimisation (continuous improvement)
- Fine-tuning of yield and throughput
- Cost reduction
- Troubleshooting (reworks, reprocessing, deviations)
- New vendor approval (use tests)
- Waste minimisation (recycling)
What is the Ideal?

“The ideal chemical process is that which a one-armed operator can perform by pouring the reactants into a bath tub and collecting pure product from the drain hole”

- Sir John Cornforth

What is the (More Realistic) Ideal for Scale-Up of a Process?

- No batch failures in pilot plant or on full-scale
- No long increases in time required for any particular stages
- Use of existing multipurpose plant equipment

*(Principles of Process Scale-Up, Lecture, Dr. Leen Schellekens, Mettler Toledo, UCD Engineering Building, 19th Oct 2004.)*
Main Issues During Scale Up and Development

(Communication and teamwork between departments. Role of process technology)
1) Chemical Development

- Selection of Synthetic Route
  - GET THE BEST ROUTE FROM THE BEGINNING - Difficult to change later
  - Route should be short, efficient, robust and give a high yield prior to scale-up
  - Discovery route often not the best. Expedient not optimal. (raw materials may not be available in bulk, process may not be efficient and may be safety hazards on large scale)
  - Compare like with like during selection (Same level of optimisation and same scale. Are products of same purity obtained? What is the cost comparison?)
  - Main constraint is TIME
Chemical Development

- Selection of Synthetic Route cont’d
  - Shortest route usually best (less effluent, shorter lead time, short plant occupation, less analytical work)
  - A convergent synthesis will be cheaper than a divergent (linear) one with the same number of steps
  - Literature not always correct and perseverance with a reaction is required
  - Better to try routes with high chance of success but those which offer significant benefits should be attempted even if little precedent
In Convergent Synthesis, sections of the target molecule are prepared and joined together to form the target molecule. A better yield than a linear synthesis with the same number of steps will be obtained. The advantage is significant if the subroutes converge close to the end of the synthesis.

2) Process Development

● Optimisation of Synthetic Route – Once Selected
  - Work up very important
  - Can steps easily be combined (telescoping)?
  - Need excellent process control and understanding of process limits (“stress” the reaction – higher temperature, longer reaction time, less efficient mixing). “Critical” steps / parameters (Quality)
  - Good analytical methods (standards)
  - Isolate and characterise by-products
  - A very innocuous process change can often have a significant influence
Costing of Processes

- Must be a standard costing procedure
- Should be dated and updated
- Assumptions should be stated
- May be several factors leading to variation – scale, plant configuration etc.
- Compare like with like and be conservative
- Carried out by independent person
- Want to be able to see which factors increase cost significantly and why
Planning for Scale-up

- Decide on process
- Decide on batch size (not too large an increase)
- Order raw materials (allow for 10% lower yield)
- Carry out safety tests (Exotherms, HAZOP – hazard and operability studies)
- Discuss the process and plant requirements with production manager/engineer (materials of construction). Existing multipurpose plant usually.
- Prepare safety data sheets and discuss handling of hazardous reagents or intermediates
- Ensure analytical procedures, equipment and staff are available
Scale-up

- Planning for Scale-up cont’d
  - Write out detailed procedure (assume nothing);
    - Cleaning check and preparative work
    - Charging and weighing
    - Temperature and time limits
    - Sampling (in-process checks)
    - Transfers
    - Work-up and isolation
    - Drying and effluent disposal/treatment

Make allowance for delays / problems (rework procedures, identify suitable “hold points”)


Scale-up

Planning for Scale-up cont’d

- Leave space in procedure to record data and observations
- Highlight safety procedures and steps to take if spillage occurs
- Provide training
Scale-up

- Significant Differences Between Lab and Plant
  - Heat transfer
  - Agitation (frothing)
  - Mass transfer (affects kinetics)
  - Visibility – of reactions, separations, for cleanliness checks
  - Separation (stirring, not shaking)
  - Time (slower addition rates and heating/cooling times, longer work up)
  - Hazards (Toxic, Exotherm and Electrostatic)
  - Off-gas treatment
  - Safe and efficient sampling techniques needed (Process Analytical Technology - Real time reaction monitoring; FT-IR, Particle size - FBRM)
**Scale-up**

- **Process Development Taking Account of Differences Between Lab and Plant Equipment**
  - Use safety data already produced to help characterise reaction
  - Study effect of scale-dependent factors (mixing, mass transfer and heat transfer) at lab scale
  - Plan a logical set of experiments in time-frame available
  - Mimic plant conditions; slower addition of reagents, slower rate of heat increase and decrease and mixing, lab system should be baffled if reactors are (no vortex)
  - Obtain mass and heat transfer data for reactor type, agitator type and solvents to be used.
  - Use simulation software to predict effects of mass and heat transfer and mixing changes on scale-up.
Scale-up - Crystallisation

- Crystallisation often causes problems
- Fine control required
- Changes in crystal habit (external structure) may affect ease of isolation, washing and drying.
- Changes in crystal form (polymorphism – internal arrangement of atoms different) affect solubility, dissolution rate, ease of isolation and drying. Affects formulation.
- Very common problem – impacts on drug activity
- (FBRM, Raman, PVM real time monitoring)
Scale-up - Troubleshooting

- Plan schedule to accommodate delays on first batches
- Develop contingency plan for incomplete reactions
- If problem occurs, establish whether is physical (physical manipulations of the processing) or chemical (process inputs)
- Examine processing steps that occurred just before problem was noted and work backwards
- Address operations that are simplest to change first
Case study; Process Development for Labetalol Production at Schering Plough Ltd., Rathdrum

BACKGROUND

- Labetalol – antihypertensive, 30,000 Kg p.a. produced by Schering-Plough.
- First 2 steps in Rathdrum, Co. Wicklow. Final step (hydrogenation) in U.S. or Puerto Rico.
Labetalol Manufacturing Process

- Mono-pot reaction in jacketed, glass-lined 10,000 L reactor.
- Addition of liquid reagents and jacket temperature computer controlled. Solid reagents charged manually via handhole.
- Phase separation using sight-glass.
- Solid product from second step isolated by centrifugation.
- Product tested to determine if recrystallisation necessary.
- When required purity achieved, product is dried.
Labetalol Process – Step 1

5-ASA

5-Br-ASA

Main impurities:

~ 5%

~ 2%

~ 1%
Labetalol Process – Step 1, Process Development

- Solvent system modified to isopropanol / ethyl acetate containing hydrogen bromide from methanol / ethyl acetate to reduce formation of third impurity. Original process used chloroform.
- Concentration was increased threefold increasing throughput and reducing solvent waste.
Labetalol Process – Step 2

5-Br-ASA + Dibenzyamine → LBH-B/C + propylene bromohydrin
Labetalol Process – Step 2, Process Development

- Large excess of dibenzylamine used to ensure reaction driven to completion (cheap reagent and easily washed out)
- Propylene oxide added as it reacts with HBr side-product as it’s produced. Presence of HBr would neutralise dibenzylamine and no reaction to give product would occur. Propylene bromohydrin side-product easily washed out.
- Use gentle reflux to ensure propylene oxide doesn’t escape
Summary

- Stages of development are Chemical Development, Process Development and Process Support
- Development essential before scale-up and validation – get process right first
- Time constraints a major factor
- Have process in control (”critical” parameters)
- Consider differences between lab and plant scale. Try to mimic plant conditions in lab to anticipate effects when scale up.
- Prepare process description carefully for scale-up
- Development always on-going
Bibliography


Bibliography cont’d


FURTHER READING:

