Project Management on API Manufacturing

Develop an Efficient Control Strategy and Implementation

Cortona
September 19th, 2010
Andrea Castellin PhD
A team committed to develop, produce and deliver high quality substances: active ingredients, key intermediates and building blocks for the pharmaceutical industry worldwide.
Interactions

FACT&FIGURES
2 manufacturing area
8 plants
1700 m3 reactor capacity
620 employees
All of them located in Italy

PMDA
Japan

SFDA
China

KFDA
South Korea

FDA
USA

AIFA
Italy

Foreign IPRs authorities
What we learn in doing this job...

- Develop a process is not only matter to deliver product to customer.
- Have a customer doesn’t justify meanings in front a patent or a regulatory body.
- Built-in quality it is not only matter to respect a guidelines.
- Do research to introduce innovation it is not only to make up your budget of investments.

Rather is ...
What we do

Make just in time
What they want
In the smoothest way

And

Eventually get to your stakeholder
A perception of quality that meet their expectations
Project management flow: planning a proposal

Pre-Evaluation Phase

Outward examination of the chemistry and technology
Collect general information
Financial and commercial data
Technical package analysis from the customer if available

Technical Evaluation:
Complexity of chemistry, stoichiometry process performance, raw material consumption, technology fitting, therapeutic equivalence and plant suitability, toxicological profile...

Economical Evaluation:
Raw material supply chain investigation, lab and Kilolab, Pilot operation, Validation and commercial scale costs evaluation, investments and budgeting

Activities

Duration

Best track: 5 working days
Best track: 11 working days

Deliverables

Formal communication to the customer of entry to next level of examination
Customer will be receive from Commercial Area Manager:
- Detailed Project plan
- Technical Presentation
- Quotation
Project handling on R&D phase

At the project kick-off meeting R&D generate a consolidate version of the project plan, re-defining activities, and the project charter, a tool intended to handle the different activities progression together with the customer. Basically the project charter collect the following flow of activities:

- **R&D Process Phase**
  - **DEFINITION R&D OBJECTIVES**
  - **PROJECT CHARTER SHEET**
  - **PROJECT MILESTONES**
  - **DEFINITION OF ANALYTICAL DEVELOPMENT**
  - **DEFINITION OF SUPPLIER RAW MATERIALS & BUILDING BLOCKS**

- **QC PROCESS**
- **LOGISTIC PROCESS**

- **Other Process contribution**
- **Deliverable Contents**

Bibliographic search
IPRs analysis report
Preliminary cost evaluation sheet
Project handling on R&D phase

Other Process contribution

R&D Process Phase

 Deliverable Contents

• Lab and Klab procedures/process description
• Lab and Klab work order
• Personnel instruction
• Data experimental collection
• Analytical method developments for IPC and target product
• Process safety analysis
• Definition of critical RSM and RMs
• Definition of plant scheme
• Lab and Klab samples
• Post production and waste treatment methods
• Hold point definition
• Solvents recovery
• RMs and intermediates impurity carry over
• Cleaning procedures
• QbD and Risk assessment
Analyzing a specific case: Olopatadine HCl

- **Olopatadine HCl** is an antihistaminic compound.
- **Patent Expiry date in Japan**: 27th February 2012
- **Patent Expiry date in Italy**: 3rd March 2007
- **In US and European Market** is sold against seasonal allergic rhinitis as *eyes drops* or *nasal spry*.
- **In Japanese market**, the compound is commercialized in *tablets* form.

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AIFA

Italy

→

PMDA

Japan
Analyzing a specific case: Olopatadine HCl

**Scope:**

- Build up a successful strategy for manufacturing and launch the product for the **generic Japanese market**
- Mind **quality requirement** for safety and efficacy of the drug, API related
- Meet target quality according to innovator’s **Interview Form**
- Mind the **business requirements** to have an accessible drug
Olopatadine HCl: chemistry background

OLOPATADINE HCl

Formula Weight  = 373.87316
Molecular Formula  = C₂₁H₂₄ClNO₃

Business impact

“Grignard reagent” approach

“Wittig reagent” approach

Quality Impact
“Grignard reagent” approach

Some of the described innovator’s pathway

Reactants and conditions:
- Thionyl Chloride
- CH₂Cl₂
- Toluene
- Ethyl Acetate
- Magnesium
- THF
- CH₂Cl₂
- NH₂OH
- HCl
- NaOH
- p-Toluen Sulphonic Acid
- Ethanol

Final API
Salt formation
Wittig reagent approach: FIS’ pathway

**STAGE 1**

\[
\text{ISOXPAC CARBOXYLIC ACID PROTECTED} \quad [1]
\]

**STAGE 2**

\[
\text{ISOXEPAC CARBOXYLIC ACID PROTECTED} \quad [2]
\]

**STAGE 3**

\[
\text{OLOPATADINE FREE BASE} \quad [3]
\]

\[
\text{OLOPATADINE HYDROCHLORIDE FINAL API} \quad [4]
\]

\[
\text{OLOPATADINE FREE BASE} \quad [5]
\]
Some key project milestones

1. April 2008, a bibliographic and patent analysis were carried out
2. June 13th 2008, FIS received from supplier the two key raw materials
3. July 31st 2008, samples of the API were dispatched to Japan
4. February 2009 after in deep patent analysis, research & development, the process reaches a definitive configuration
5. June 2009 a “DEMO Batch” of Olopatadine HCl was produced
6. After the synthesis of the DEMO Batch some synthetic parameters were revised and minor process changes were introduced. Changes were applied in several Lab trials and as result overall yield of the process was increased.
7. December 2009: Validation Campaign was performed
Project management: plan assumptions

**Basic requirements**

- 3 stages chemistry
- 2 main chemical transformations and other expertise required
  - *Ester formation*
  - *Wittig/Ilide addition*
  - *Salt break up*
  - *Crystal abit, polymorphism control*
  - *Psd control*
- 2 isolated intermediates/final product
- Micronization required
- Process development and front run Kilolab sample required by the customer
- Qualification batches
- Validation batches
- DMF filing
Project management: actuation plan

Project kick-off meeting activities

- **Duration**: 6 wd
- **Deliverable**: IPRs analysis
  - Definition of technical requirements

**Supply Chain RMs**

- **Duration**: 38 wd

**Analytical Dept. activities**

- **Duration**: 32 wd (analytical dev.)

**Process Development**

- **Duration**: 46 wd

**Plant Setup**

- **Duration**: 20 wd

**Qualification batch Pilot plant**

- **Duration**: 40 wd

**Quality Assurance activities**

**Deliverable**

- Supplier Qualification
  - Competitive intelligence analysis

- Raw material - Comparison test and specifications
  - Analytical development
  - Technology transfer/Method validation
  - Stability studies (second stage)

- Familiarization studies
  - Process safety evaluation
  - Front run sample from lab to Klab
  - Project reporting (weekly and TCs)
  - Solvent recovery studies and other economical impact evaluation
  - QbD analysis

- MBRs
  - Project reporting (weekly and TCs)
  - Campaign report

**wd**: working days

Next stage
Project management: actuation plan

**Previous stage**

- **Qualification batch**
  - **Pilot plant**
  - Duration: 40 wd

**Validation Campaign**

- **Commercial plant**
  - Duration: 62 wd

**Quality Assurance activities**

- Duration: 245 wd
  - Deliverable: MBRs
  - Deliverable: Project reporting (weekly update)
  - Deliverable: Campaign report
  - Deliverable: Validation report
  - Deliverable: Link to QA activities
  - Deliverable: cGMP customer audits on site
  - Deliverable: Batch releases
  - Deliverable: Validation summary report
  - Deliverable: DMF preparation and submission to Italian Health Authority (AIFA)
  - Entering the phase of review period by AIFA (120-180 days)

**Total Duration**

- 300 working days, from the kick-off meeting

**Dispatch of validation batches**

*wd: working days*
Define a strategy

- Audit/knowledge supplier process
- Build up a supply chain setting the appropriate specs
- Raw materials impurities
- Use of DoE
  - Define a risk assessment table
  - PARs determination
  - PARs verification
- Process related impurities
- Drug substance CQA
- QCPPs
- Process understanding
## Risk assessment table

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Residual Solvents</th>
<th>Residual Raw Material / Intermediates</th>
<th>Residual Metal / Bromine content</th>
<th>Degradation / new impurities</th>
<th>reaction by-products</th>
<th>API form / PSD</th>
<th>Yield</th>
<th>Batch Size Productivity</th>
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<tbody>
<tr>
<td>Ilide formation</td>
<td>✅</td>
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<td>Seeding / Crystallization as Free base</td>
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<td>DMF Amount in Purificatoin of Olopatadina Free Base</td>
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<td>HCl Salt formation / Crystallization</td>
<td>✅</td>
<td>✅</td>
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</table>
Ishikawa diagram of the process
Ishikawa diagram of the process

<table>
<thead>
<tr>
<th>Process Steps</th>
<th>Seeding</th>
<th>Amount Required</th>
<th>Water Amount</th>
<th>KOH Equivalents</th>
<th>Dilution</th>
<th>Temperature</th>
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<tr>
<td>Crystallization as Free Base</td>
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<td>HCl Salt Formation</td>
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<td>Hydrolysis</td>
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</tbody>
</table>
Set up a DoE study

A road map for the investigation

DoE as a tool
<table>
<thead>
<tr>
<th>Parameter Investigated_1</th>
<th>Min.</th>
<th>Max.</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaH Equivalents (referred to Isoxepac Butylester)</td>
<td>2,1 eq.</td>
<td>3,3 eq.</td>
<td>2,5 eq.</td>
<td>2,7 eq.</td>
</tr>
<tr>
<td>Phosphonium Salt Equivalents</td>
<td>1,1 eq.</td>
<td>1,5 eq.</td>
<td>1,2 eq.</td>
<td>1,3 eq.</td>
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<td>Reaction Temperature</td>
<td>10,0 °C</td>
<td>50,0 °C</td>
<td>38,0 °C</td>
<td>42,0 °C</td>
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<tr>
<td>Total solvent Amount</td>
<td>6,0 V</td>
<td>12,0 V</td>
<td>7,0 V</td>
<td>9,0 V</td>
</tr>
<tr>
<td>KOH Equivalents (referred to Isoxepac Butylester)</td>
<td>0,7 eq.</td>
<td>1,1 eq.</td>
<td>0,8 eq.</td>
<td>0,9 eq.</td>
</tr>
<tr>
<td>Dilution (Methanol Water = 1.8 : 1)</td>
<td>18,0 V</td>
<td>26,0 V</td>
<td>19,0 V</td>
<td>23,0 V</td>
</tr>
<tr>
<td>Reaction Temperature</td>
<td>20,0 °C</td>
<td>75,0 °C</td>
<td>60,0 °C</td>
<td>70,0 °C</td>
</tr>
<tr>
<td>Total solvent Amount</td>
<td>3,0 V</td>
<td>6,0 V</td>
<td>3,5 V</td>
<td>4,5 V</td>
</tr>
<tr>
<td>Filtration Temperature</td>
<td>-15,0 °C</td>
<td>20,0 °C</td>
<td>0,0 °C</td>
<td>5,0 °C</td>
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<tr>
<td>Acetone Total Amount (dilution in Volumes referred to Olopatadine Free Base)</td>
<td>15,0 V</td>
<td>25,0 V</td>
<td>17,0 V</td>
<td>20,0 V</td>
</tr>
<tr>
<td>Water Amount (dilution in Volumes referred to Olopatadine Free Base)</td>
<td>0,0 V</td>
<td>1,5 V</td>
<td>0,5 V</td>
<td>0,8 V</td>
</tr>
<tr>
<td>HCl Amount</td>
<td>1,0 eq.</td>
<td>2,0 eq.</td>
<td>1,4 eq.</td>
<td>1,6 eq.</td>
</tr>
</tbody>
</table>

**Proposed Critical Process Parameters**
### Other Process parameter ranges for the process

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Min.</th>
<th>Max.</th>
<th>Min.</th>
<th>Max.</th>
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</thead>
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<tr>
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<td>79.0 °C</td>
<td>75.0 °C</td>
<td>79.0 °C</td>
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<tr>
<td>Methyl THF amount (in Volumes referred to Isoxepac Butylester)</td>
<td>5.0 V</td>
<td>6.5 V</td>
<td>5.7 V</td>
<td>5.9 V</td>
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<tr>
<td>Reaction Time</td>
<td>3.0 Hrs</td>
<td>8.0 Hrs</td>
<td>4.0 Hrs</td>
<td>6.0 Hrs</td>
</tr>
<tr>
<td>Water Amount</td>
<td>3.0 eq.</td>
<td>6.0 eq.</td>
<td>4.0 eq.</td>
<td>4.5 eq.</td>
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<td>Phases separations Temperature</td>
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<td>30.0 °C</td>
<td>20.0 °C</td>
<td>25.0 °C</td>
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<tr>
<td>Maximum Concentration Temperature</td>
<td>60.0 °C</td>
<td>50.0 °C</td>
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<tr>
<td>Methanol Amount</td>
<td>12.0 V</td>
<td>20.0 V</td>
<td>14.0 V</td>
<td>16.0 V</td>
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<tr>
<td>Water Amount</td>
<td>5.0 V</td>
<td>10.0 V</td>
<td>7.0 V</td>
<td>9.0 V</td>
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<tr>
<td>Reaction Time</td>
<td>2.0 Hrs</td>
<td>8.0 Hrs</td>
<td>2.0 Hrs</td>
<td>4.0 Hrs</td>
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<td>Maximum Concentration Temperature</td>
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<tr>
<td>Maximum Concentration Temperature</td>
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<tr>
<td>Seeding Amount / Quality</td>
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<td>0.005 W</td>
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<td>Filtration Temperature</td>
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<td>Drying Temperature</td>
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<td>Ilide Formation</td>
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</table>
Conclusions

- Structural approach to gain process knowledge
- Developing robust manufacturing control strategy
- Give space to innovation to fulfill the robustness
Acknowledgement

Old wood and science

Clark Ferrari, Project Leader, Olopatadine HCl
Marco Galvagni, Divisional Director R&D
Thank you!

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