APIs (manufactured by Chemical synthesis)

Presented by Rajeev Patil

in conjunction with PharmSol Group Limited

We will be talking.....

- Introduction
- Typical Manufacturing process and equipment used for APIs
- Key Manufacturing issues specific to APIs & how they relate to GMP issues
- What to see during DMF review?
- How to inspect API facility?

Just a suggestion !

Introduction

- Manufacturing of APIs is unique & quite different as compared to the drug products
- APIs are manufactured by
  - Chemical synthesis
  - Fermentation (conventional & recombinant DNA)
  - through Enzymatic conversions
  - recovery from natural materials
  - Semi-synthetic process
- API manufacturing plants are designed and constructed in different ways depending on:

➢ the chemistry

➢ the nature of the API: “normal” or potent, Cytotoxic, B-lactams, Hormones, etc.

➢ country, climatic region

➢ “old” plants or “state-of-the-art designed” new plants

Introduction

- API plant has main parts such as –

❖ Synthesis & Processing plant with necessary Controls for -
  - Weighing of raw materials , “Lot Preparation” (Dispensing)
  - Chemical processing , Isolation , processing of Intermediates, etc.
  - Storage of Intermediates, in-process materials, recovered solvents, Mother Liquor(ML), etc.

❖ Controlled /Clean area with controls similar to any Oral drug product facility for-
  - Final step of processing e.g. Purification of Crude to pure API
  - Crystallization/Precipitation of the API
  - API Isolation - Centrifugation /Filtration, spray drying
  - Drying & further Processing- Milling, Micronization, Compaction, Sifting, Blending /Homogenization, Packing, labelling, etc.

❖ Storage facility for RMs, Packing materials, Finished APIs, Solvents & Hazardous Chemicals

❖ Solvent recovery plants

❖ Utilities/ Critical Support Systems plants for -Purified Water generation, steam generation, compressed air supply, Nitrogen supply, HVAC system, etc.

❖ Quality Control laboratory, In-process controls area, Quality Assurance department

❖ Engineering, maintenance area , Effluent treatment facility

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Inside a Typical API Plant

Clean Room for Highly Potent API

Typical Manufacturing Process and Equipment used for APIs

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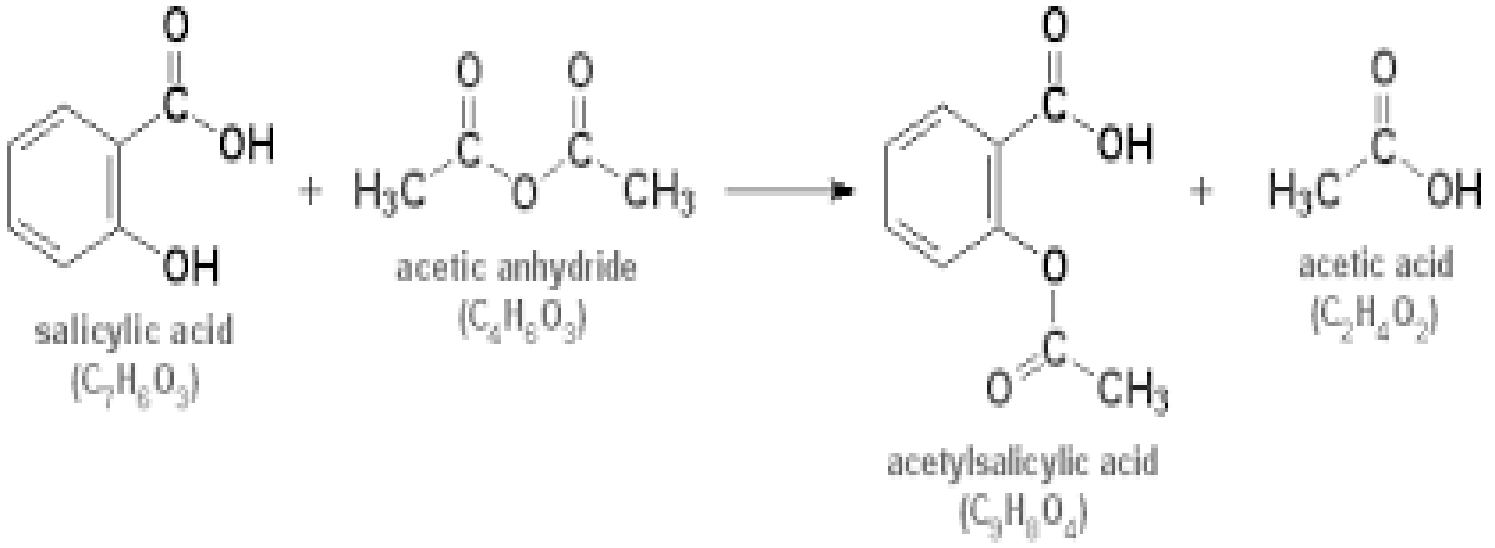
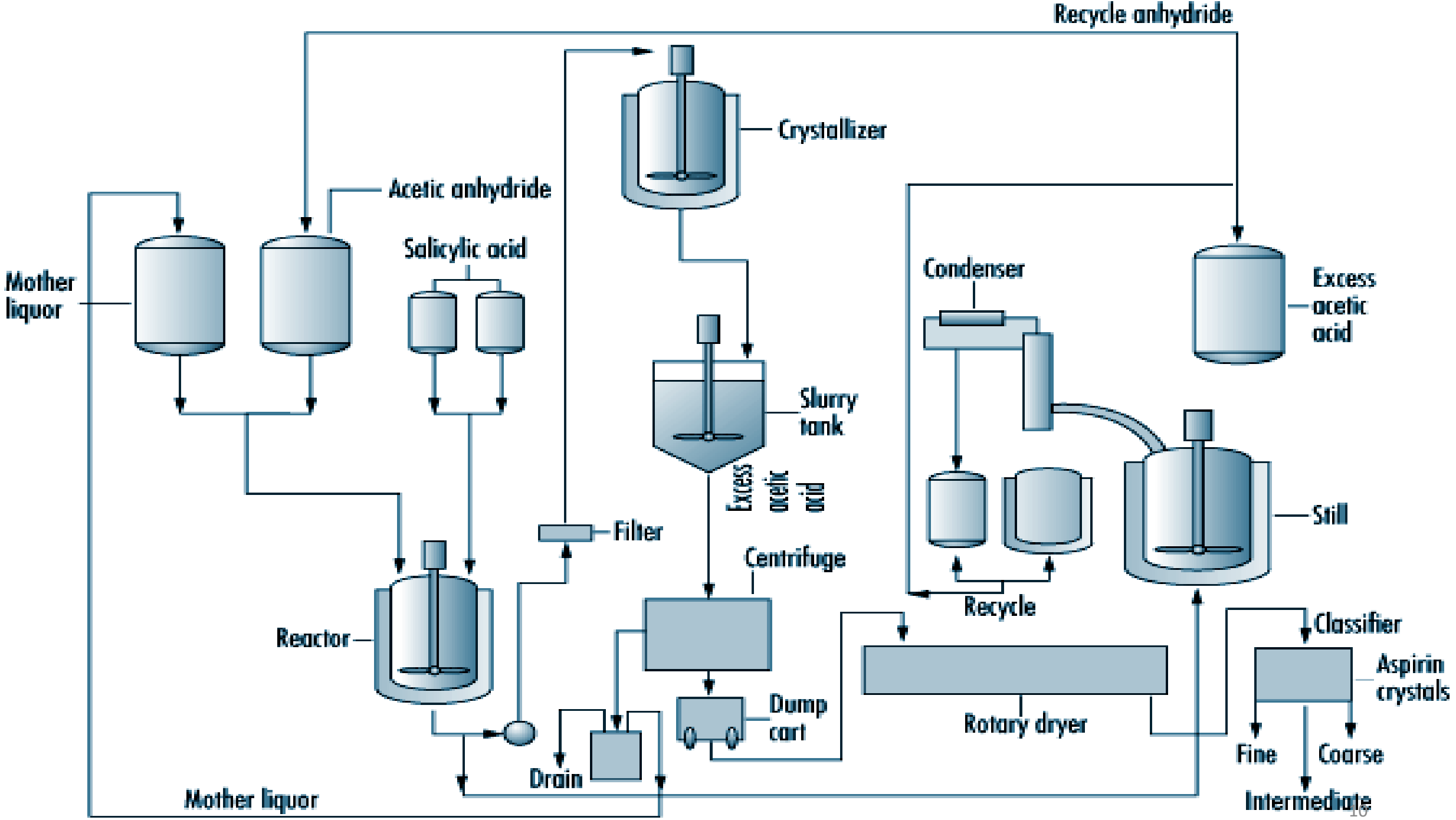
- Manufacturing process of API can be simple or complex depending upon:

- Number & types of synthetic steps, processing steps
- Types of chemical reactions & processes –Low or high temperature reactions, hazardous reactions e.g. hydrogenation, racemic separations, specific polymorph formation/separation
- Types of controls required for Critical Process parameters to avoid formation of unwanted Impurities, by-products, to get specific PSD, etc.

Single Step Process – Synthesis of Aspirin



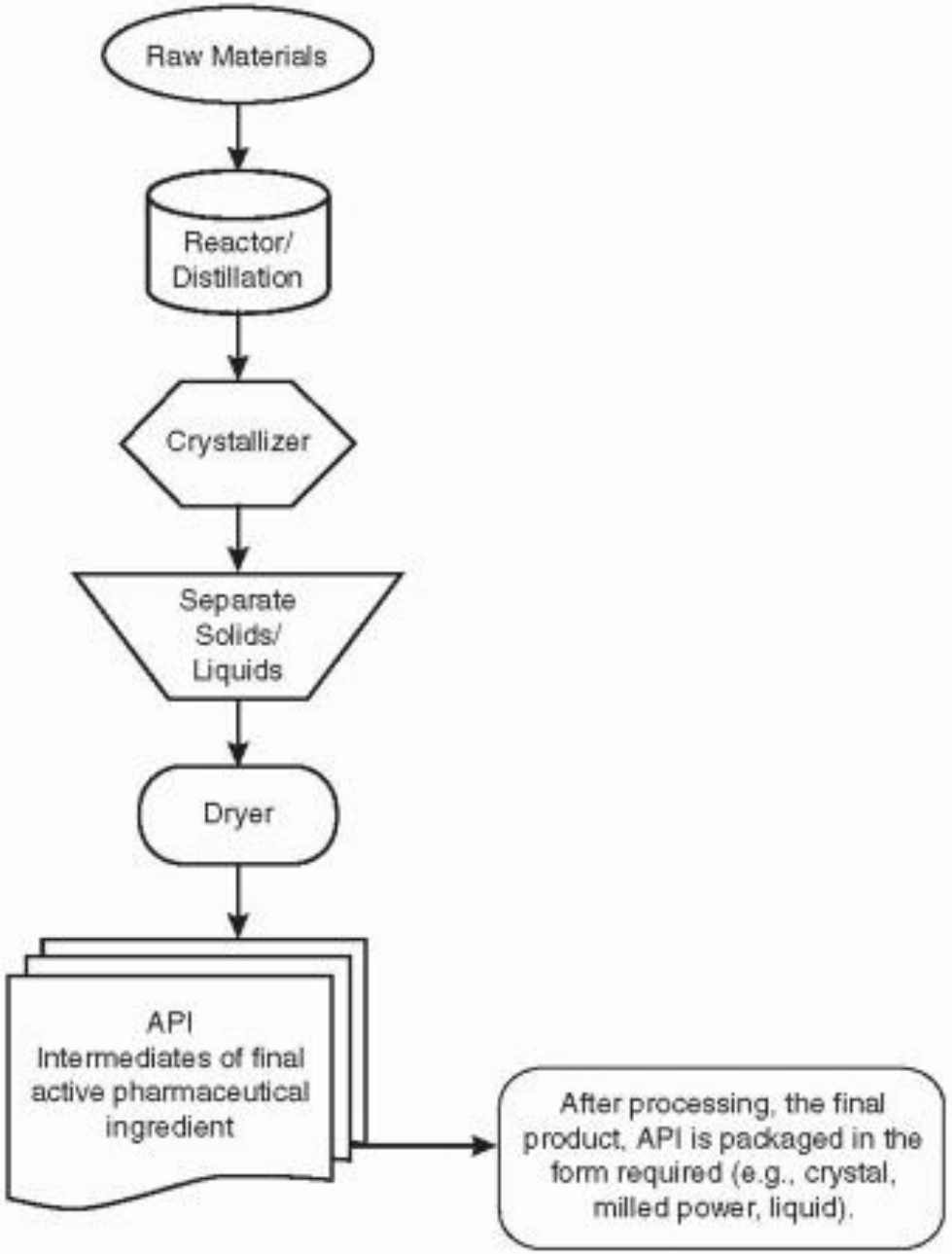


Source: EPA 1993.

Small Molecule Production

Processes Include:

- Synthesis
- Distillation
- Extractions
- Crystallization
- Purification
- Filtration
- Drying
- Milling



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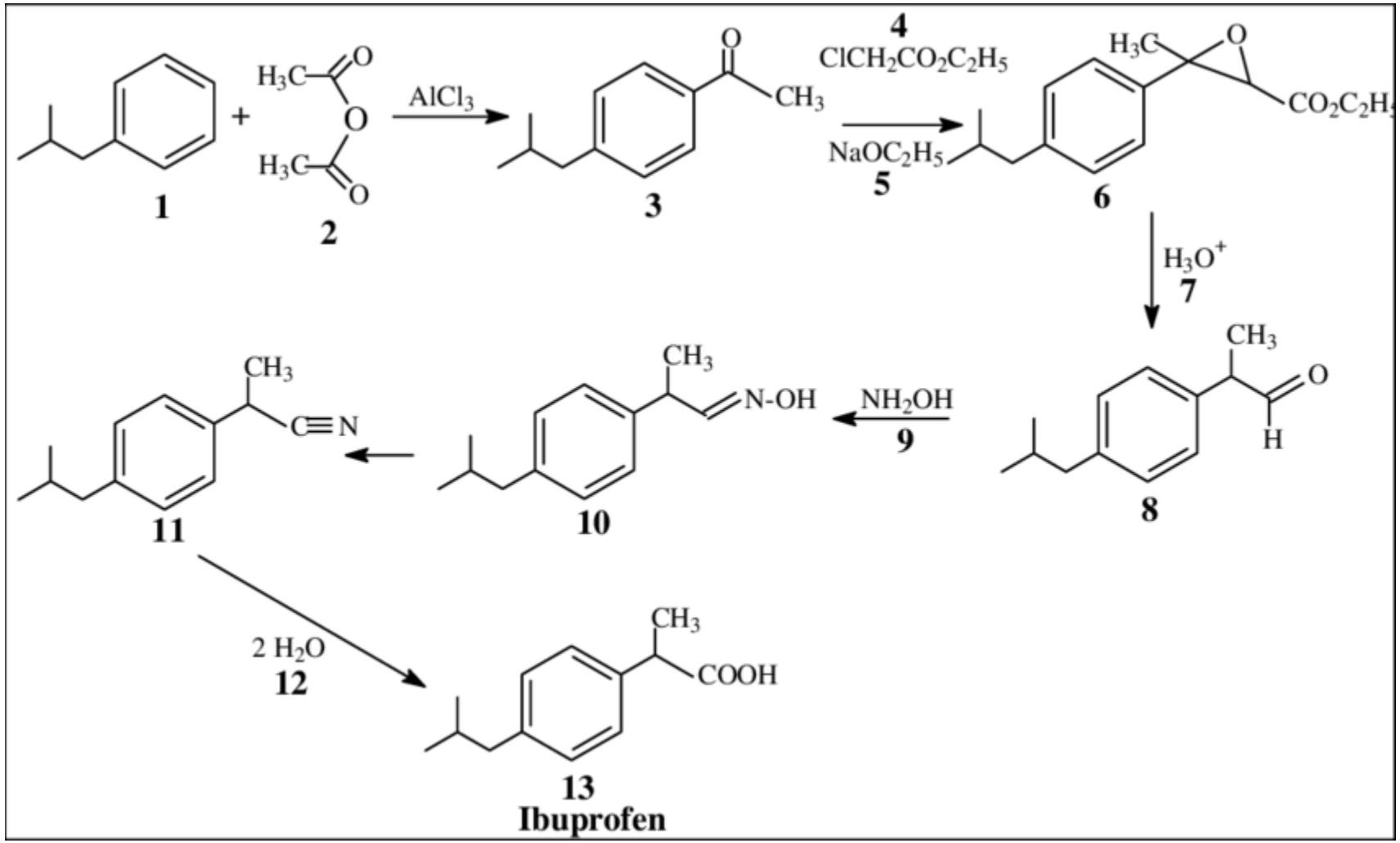
Typical API/Intermediate processing sequence

Conventional synthesis of Ibuprofen



Typical Manufacturing Process and Equipment used for APIs

- **Broadly manufacture of API made by Chemical Synthesis may involve key steps like**

➢ Dispensing ('Lot preparation')-Weighing of raw materials

➢ Transferring of raw materials-Starting Materials or intermediates, reagents, solvents, catalysts, etc to reactors

➢ Chemical reaction/transformation in reactor

➢ pH adjustment ,other in-process Controls

➢ Distillation/Evaporation of solvent

➢ Distillation /Fractionation to get pure fractions

Typical Manufacturing Process and Equipment used for APIs

- **…….Key steps (Continued)**

➢ Extraction using solvent

➢ Layer separation, filtration , clarification

➢ Resolution of racemic mixture/Separation of optical isomers

➢ Separation of different compounds using Column Chromatography

➢ Spray drying of solutions/slurries

➢ Precipitation, Crystallization in reactors

➢ Filtration-Vacuum or pressure, Centrifugation of solids

➢ Purification by dissolving in solvent, decolourization, Recrystallization of solids

➢ Drying of solids

➢ Sifting, Sieving

Typical Manufacturing Process and Equipment used for APIs

- **…….Key steps (Continued)**

➢Milling, Micronization to reduce particle size

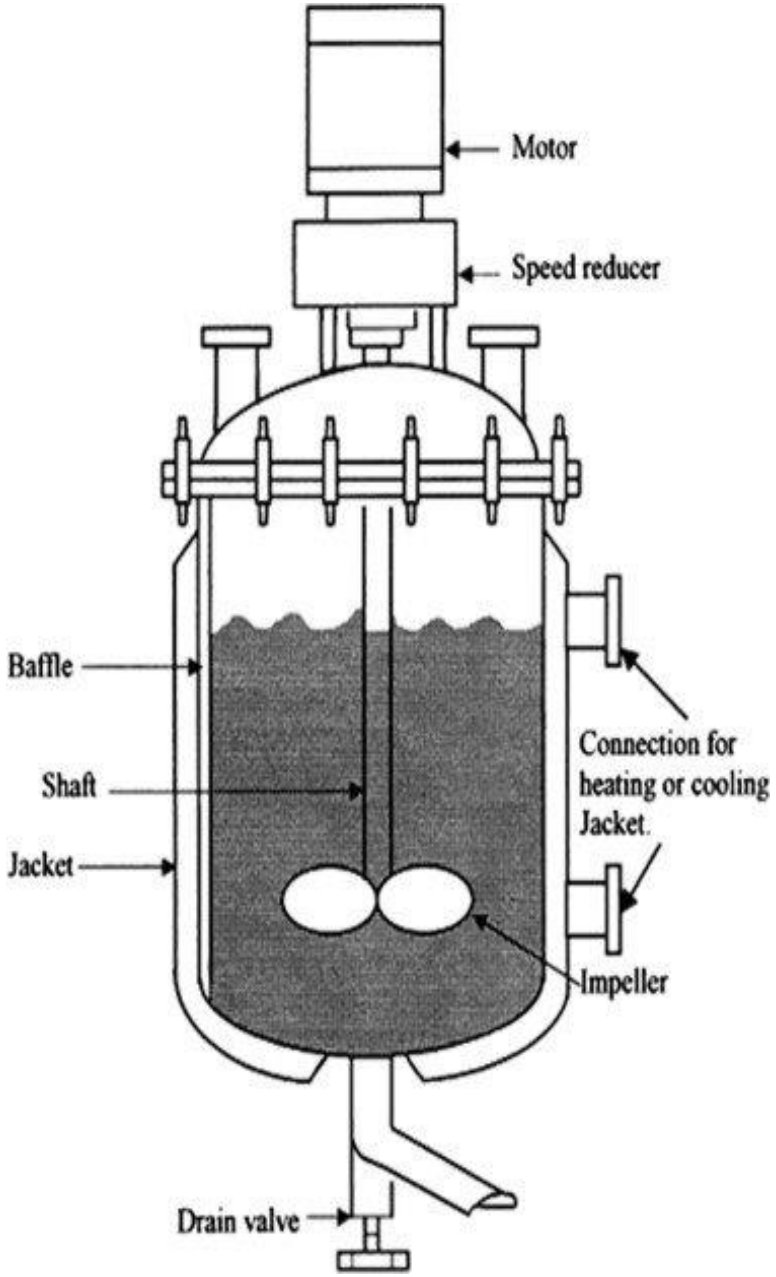
➢Compaction to improve bulk density

➢Homogenization, blending of small lots

➢Packing-Primary ,secondary & labelling

➢Storage- Controlled room temperature, or < 25℃ , Refrigerator temperature 2-8 ℃, Cold room temperature below 0 ℃

➢Transport in above referred temperature conditions



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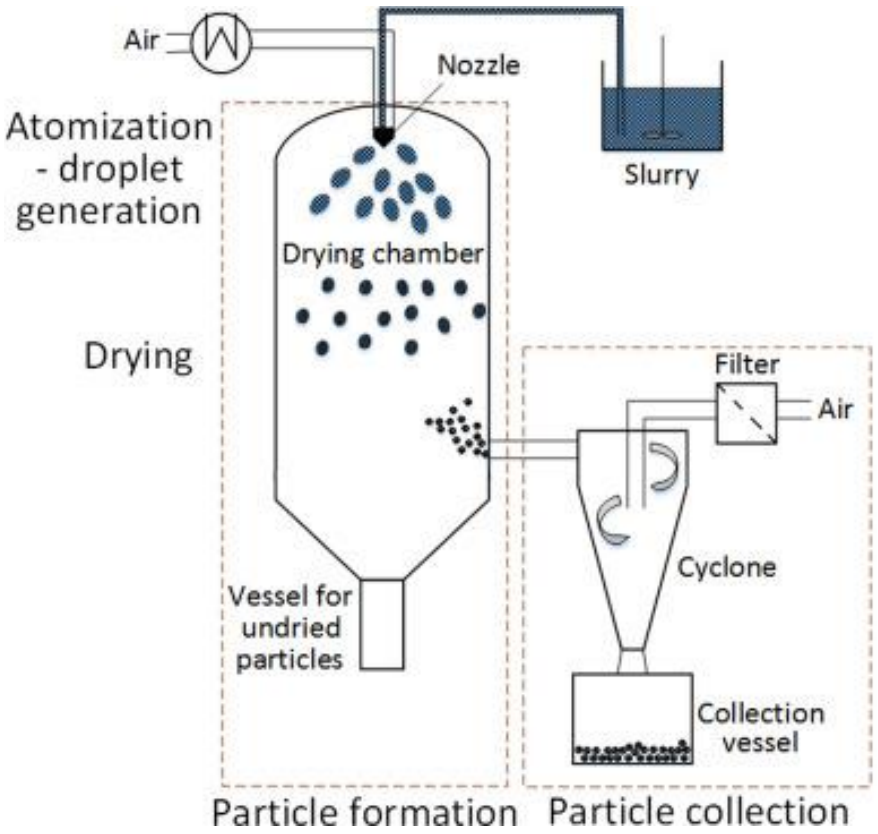
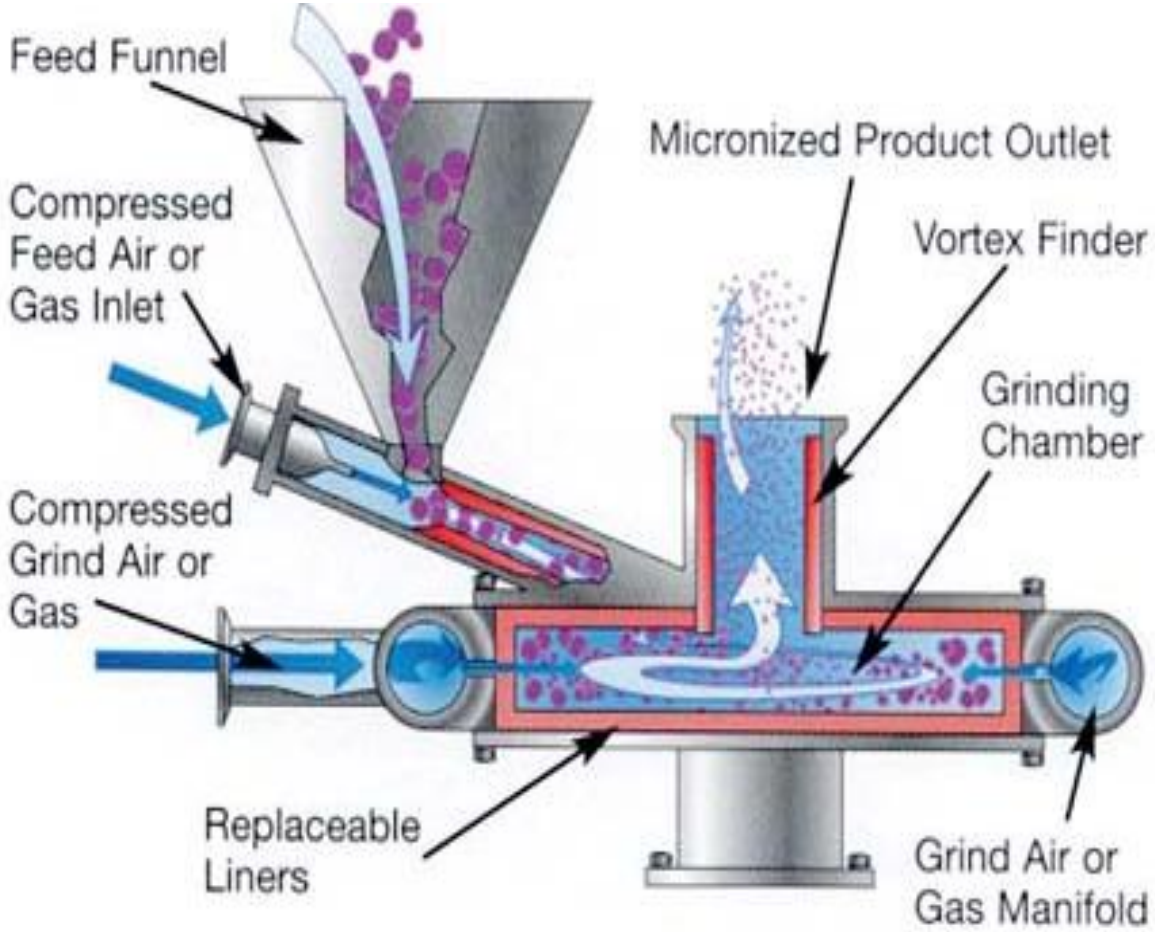
A Typical GL Reactor for API Reactions

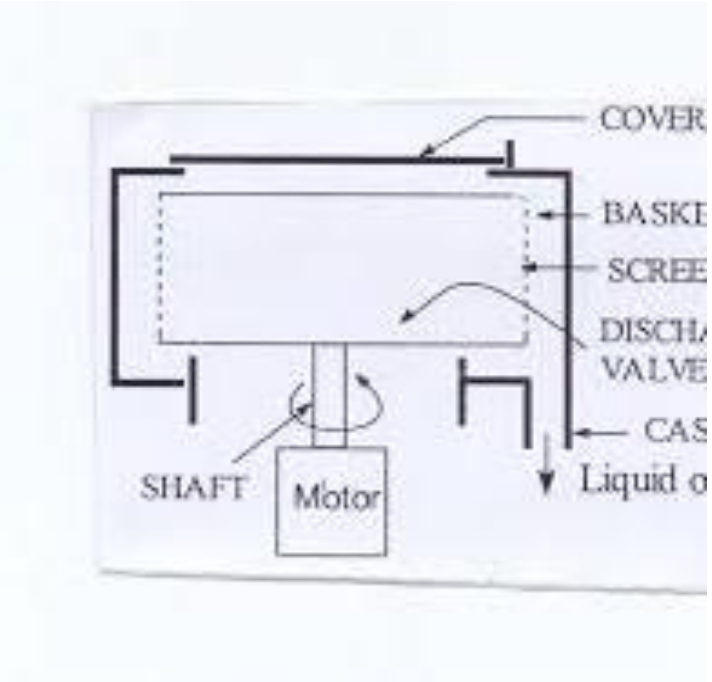

Air
Nozzle
Slurry
Atomization - droplet generation
Drying chamber
Drying
Filter
Air
Cyclone
Vessel for undried particles
Collection vessel
Particle formation
Particle collection

Spray Dryer

A Typical Air-Jet Mill



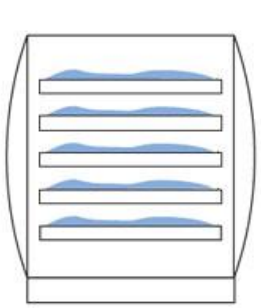
Agitated Nutsche Filter



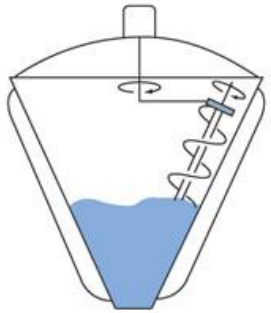
Centrifuge

Drying Equipment

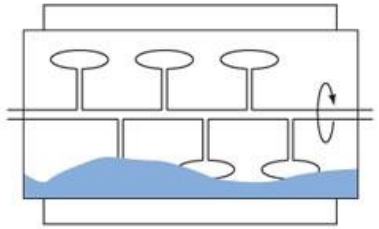
Common Types of Contact Drying Equipment



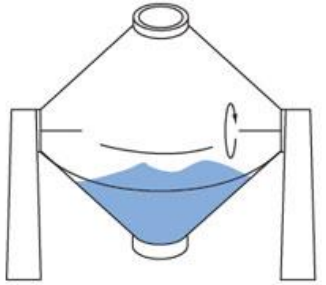
Vacuum Tray Dryer
Simple, labor intensive,
long drying times.
Potential for encrustation/poor uniformity.
Post-treatment often required.



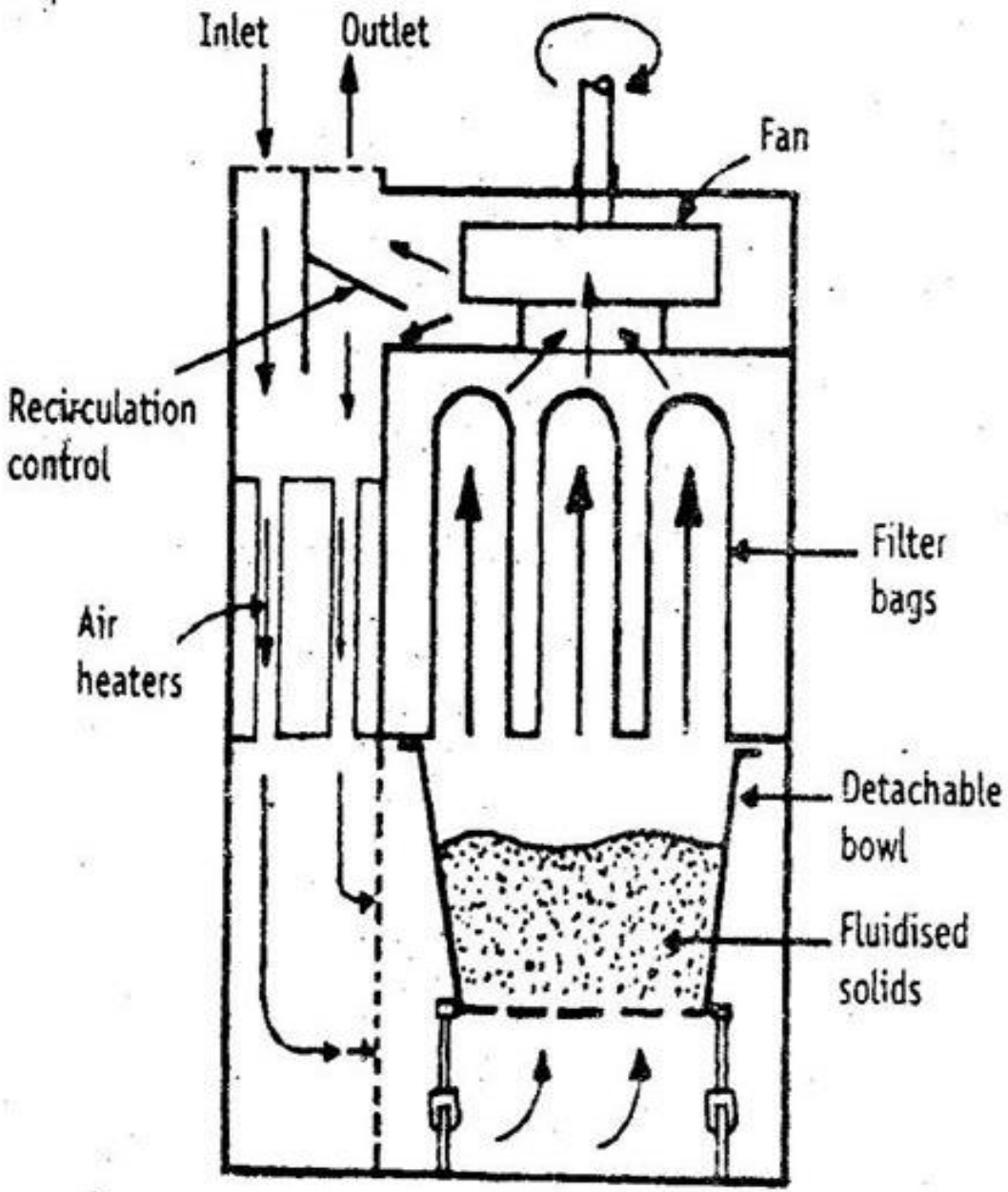
Rotary Cone Dryer
(orbiting screw)
Active agitation,
good homogeneity, but
high particle attrition.



Paddle Dryer
Medium agitation,
good homogeneity,
less attrition.



Tumble Dryer
(rotating double cone)
Gentle agitation, good
product homogeneity.
Potential for agglomeration.



Fluid Bed Dryer

Double Cone Blender

Key Manufacturing issues specific to APIs & how they relate to GMP issues

- Uncontrolled Changes in the Quality of raw materials, Starting Materials, Intermediates by supplier -
  - can have Devastating impact on consistency of quality of subsequent intermediates & API-
  - Purity, Impurity profile, formation of new Impurity, residual solvent etc.
- Inadequate Controls or no controls on Critical Process Parameters during manufacturing can affect -
  - Purity
  - Impurity profile , new impurity
  - Residual solvent levels
  - level of undesirable optical isomer
  - Change in Particle Size Distribution(PSD) of API
  - Change in polymorphic composition of API
  - Result into Low yields
  - May affect Stability of the product or intermediates
  - No. of deviations
  - No. of Batch failures

Key Manufacturing issues specific to APIs & how they relate to GMP issues

- Mixing of untested batches or “problem” batches of API –

  - Traceability issue. Batch failure

- Established Equipment Cleaning procedure not followed, Cleaning process not validated, Acceptance Criteria of residue is not based on the prevailing guidance i.e. HBEL are not considered – Contamination of other batches or other products

- Water tanks & Pipes not sanitized properly & periodically – Biofilm formation & microbial failures

Key Manufacturing issues specific to APIs & how they relate to GMP issues

Maintenance of plant equipment, Critical support systems , Corrosion – Particles , colour residues in product.

- Improper storage of Starting Materials , Intermediates & API (not in line with Hold-time , stability studies) – Shortening of life, API / intermediates Batch failures
- Improper Control on transport of APIs - Can affect stability of API, rejection by customer
- Reprocessing or Reworking of API without adequate studies/validation – it can affect Quality & Stability of API, rejection by customers
- Recovery of intermediates, or the API from mother liquor or filtrate carried out without adequate studies/validation-

  - New impurities may arise & other quality parameters may get affected.

Key Manufacturing issues specific to APIs & how they relate to GMP issues

- Inadequate Controls on recovery of solvents-

  -Recovered solvents may be source of impurities in API or intermediates , if not controlled properly.

  e.g. Warning letter from FDA to a contract solvent recovery firm as they were source of Nitrosamines impurities in “Sartan” APIs (Losartan, Valsartan) manufactured by many companies

- Cross-contamination of APIs because of faulty plant design or inadequate controls (Personnel discipline, gowning, etc.) –

  - Can result into Recall of product or Returned Goods from customers

What to see during DMF review?

- **Major points focussed during DMF review :**

➢ General Properties

- solubility in different solvents, in buffers at different pH(1,4.5,6.8,7.5)
- Hygroscopicity - Direct linkage with control of humidity in manufacturing area, primary packaging, stability, storage
- photosensitivity- linkage with handling on production area
- pKa, melting point
- Isomers – how they are separated ? –linkage with process ,selective isolation
- Polymorphism- linkage with Controls during Crystallization , storage, transport

➢ Structural elucidation, confirmation-Elemental analysis, UV, IR, NMR, MS, etc.

➢ Chemical Synthetic Scheme, Detailed Flow Charts –

- DMF holder provides a justification on how proposed Starting Material (SM) is appropriate as per ICH Q7 & Q11? If not, reviewer ask to redefine it & provide detailed information from earlier steps. It can become GMP issue also

What to see during DMF review?

- **Major points focussed during DMF review :**

➢ Addresses of sites of manufacture of SM, Intermediates & information on the synthesis of SM –It will help reviewers /inspectors about site of inspection

➢ Manufacturing details, equipment numbers, in-process controls, control of Critical Process parameters, Executed Batch Records ,etc.

- Lack of details & or poor description of manufacturing process

➢ Control of Raw materials , Intermediates , COAs

- Inadequate or missing specifications , including specifications of impurities, recovered solvents ,purity/Assay

What to see during DMF review?

- **Major points focussed during DMF review :**

➢ **Impurities**

- The carry-over of starting materials, Intermediates & their impurities, reagents, residual solvents, into the final API to be discussed
- Potential impurities & degradants need to be adequately controlled by the API specifications and analytical methods according to ICH Q3A,Q3B ,Q3C & Q3D guidelines
- The potential degradation pathways of the API to be discussed
- Discussion on potential genotoxic impurities, justification of limits according to ICH M7 guideline – e.g., Nitrosamines in Sartrans, Metformin,Ranitidine ,etc. are 'real villains' for the last 2/3 years

What to see during DMF review?

- **Major points focussed during DMF review :**

➢ Specification and Justification of Specification of API

➢ Analytical Procedures and Validation of Analytical Procedures

➢ Analytical methods transfer from R & D to site laboratory

➢ Batch analysis of API at least 3 batches- to Check consistency

➢ Reference Standards-origin, for non-pharmacopoeal RS –how it is prepared, Characterized

➢ Container-closure system-description, specifications, Declarations for primary PM i.e. generally Polyethylene bags – Food grade material , Compliance with FDA's Indirect Food additives (-Olefin -21 CFR 177.1520) guidance & EU's guideline on Immediate Plastic Containers (CPMP/QWP/4359/03 EMEA/CVMP/205/04)

➢ Stability studies of API – Is it as per ICH guidelines & applicable climate zones ? Is it packed in Simulated market containers, material is same ? , thickness?, If applicable, packed with head-space Nitrogen?, properly sealed ?

How to inspect API facility?

- **Key points to be focussed:**

❖ **General**

✓ Keep in mind all the time → *GMP requirements as per ICH Q7 are applicable from '* ***Introduction of the API starting material into process'***

→-----Increasing GMP Requirements-------→

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging

✓ As suggested in ICH Q11 , determine the intended use of the APIs in the type of drug product (topical, oral, injectable, inhalation, etc.) → It will help to decide what additional processing & testing of API needs to be done e.g., API for Injectable -controls for endotoxin & microbial limits, Inhalation products- Special Particle size Distribution, Microbial control

How to inspect API facility?

❖**General (Continued)**

- ✓ Determine the number of different APIs produced at the site
- ✓ Determine the classification of the APIs (B-lactam antibiotics, hormones, cytotoxics, etc.) manufactured in the facility.→ If APIs are potent or highly toxic, determine the containment measures
- ✓ Dedicated or multiproduct plant or runs on campaign basis →Controls to avoid cross-contamination
- ✓ Was manufacturing plant used earlier for other category 'objectional' products? How was decontamination done? → Check Report.
- ✓ For each API, ask- grade (compacted, micronized, crystalline, amorphous, etc.), batch size and number of batches produced per year

How to inspect API facility?

❖**General (continued)**

✓ Review recent major changes (new product, equipment, building renovation or extension, etc.)

✓ **Periodic Product Quality Review (PQR)** reports will give lot of clarity about various aspects. We have covered more about it in the Quality section.

→ Many inspectors start with PQR after general discussion

How to inspect API facility?

❖ **Materials & related areas**

✓ Study Starting materials & intermediates Approved Vendor List –

- Review vendor approval process
- Periodic audits of suppliers
- Technical/GMP agreement with suppliers
- Are changes carried out through Change Control Procedure?

✓ Storage areas of RMs, Intermediates (Are storage conditions-Temp & RH-are in line with Hold-time studies)

✓ Recovered materials, mother liquors- Quality? ,Storage in line with Hold-time studies ?

✓ Recovery of solvents, storage of fresh & recovered solvents, testing, controls - usage in same API step, control on contract solvent recovery units

How to inspect API facility?

❖ **Materials & related areas**

✓Weighing & storage area: lots preparation(dispensing) of KSM, RMs, intermediates

– Any possibility of cross contamination, mix-up?

- Temp & humidity controls adequate?

- Temp mapping carried out?

✓If solvents are delivered in <u>non-dedicated</u> tankers, firm should provide assurance of no cross contamination through:

- Certificate of cleaning

- Testing for trace impurities

- Audit of the supplier

✓ Contract with transporter of API or intermediates to meet appropriate transport & storage conditions.

How to inspect API facility?

❖**Buildings & Facilities**

✓Review detailed lay-out of the site , plant or plants involved in the manufacture

✓Check ventilation, air filtration and exhaust systems are provided, where appropriate & they are designed and constructed to minimize risks of contamination and cross-contamination

- Where APIs are exposed to the environment, there should be control of air

pressure, microorganisms (if appropriate), dust, humidity, and temperature.

Generally, these areas are supplied with HEPA filtered air

✓Check utilities that could affect product quality e.g., steam, Nitrogen or other gas, compressed air, HVAC system are qualified and appropriately monitored.

How to inspect API facility?

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❖ **Buildings & Facilities**

✓ Design of equipment washing & drying areas-

- Separate areas for dirty hold & Clean equipment ?
- Utilities (type of water, Compressed air, etc.) are supplied

Water

✓ Source of water-river, lake, well?

- Is treatment done validated ?
- Check process water, at a minimum, meet WHO guidelines for drinking (potable) water quality

✓ For some APIs, Purified Water may be required

- Check Qualification of purified water generation system

➢ How periodic sanitization is carried out for water storage & distribution system

➢ Review trends of water (Potable & Purified) testing data.

How to inspect API facility?

- **Production & related points**

✓Assess whether there are adequate controls during reactors charging, subsequent processing, handling of intermediates, in-process products, etc.

✓Environmental & GMP controls increase more towards final API formation & processing - final reactor, centrifuges, dryers & other processing equipment like mills, micronizer, compactor, blender, & packing, labelling area.

✓To get “feel” of API manufacturing Process:

- Review complete Synthetic scheme including Short names used.
- Review detailed flow chart of manufacturing of all steps including names of all reagents/ reactants & reaction conditions.

How to inspect API facility?

- **Production & related points**

✓Are manufacturing process details submitted in DMF & those existing in the production area are same-

- Compare executed BPRs from DMF with production floor BPRs
- Compare equipment numbers ,types
- Are In-process checks correctly done?
- Are all activities directly recorded, checked & signed at the time they are performed?

✓If any of the manufacturing operations, intermediates or services, are outsourced, understand the name and address of the subcontractors, service providers →Check Technical /Quality agreements, audit reports, CAPAs.

✓Review Cleaning Validation approach- Entire train of equipment or individual equipment?, Clean-in-place (CIP) ,maximum allowed carry over calculation – based on HBEL ?, Limits rationale?, Sampling?, Validation of analytical method, Recovery studies , Maximum allowed Dirty Hold Time & its validation.

How to inspect API facility?

- **Quality**

✓**Periodic Product Quality Review (PQR)** reports will give lot of clarity on :

- Trends of Critical quality test results, Critical in-process controls
- Batch failures
- Critical deviations/nonconformances & related investigations
- Changes carried out in the processes , methods, key suppliers, etc.
- Results of stability studies
- Quality-related returns, complaints, recalls
- Adequacy of Corrective actions

How to inspect API facility?

- **Quality**

✓ **Reserve/Retention samples**

- To be retained for each batch of API for 1 year after the expiry date of the batch, or for 3 years after distribution of the batch, whichever is longer
- To be stored in the equivalent to the marketed packaging system or in the more protective one

✓ **Stability Studies**

- Are adequate number of API samples packed in simulated market containers? If applicable, is it packed under Nitrogen?
- If API is micronized, is it subjected to stability studies?
- Is stability studies carried out to support major changes introduced to the processes, suppliers or analytical methods ?
- Is temperature mapping carried out for stability ovens?

How to inspect API facility?

❖ **Quality** (continued)

✓ How **Quality Risk Management** principles are applied in areas which are key for API manufacture-

- Impact of control on the manufacture of Starting Materials, intermediates(from suppliers) on the quality & stability of API
- Control on Critical Process Parameters & Critical Material Attributes
- Facilities design & Construction for Cross-contamination, Microbial contamination, Product mix ups , flow of men & material
- Control on cleaning of equipment
- Storage & transport of RMs, intermediates, mother liquors & API

How to inspect API facility?

❖ **Quality (continued)**

✓Returned Goods handling

- How returned APIs or intermediates from customers are handled- transported, quarantined ,tested, reprocessed /reworked or disposed off?

How to inspect API facility?

- We have not talked about areas which are very similar to Drug Product Inspection:

✓Site Master File

✓Validation Master Plan

✓Qualification of facility ,equipment, utilities,

✓Preventive Maintenance

✓ Calibration of measuring instruments

✓ Validations of analytical method

✓Transfer of analytical methods from Development to testing sites

✓Process validations

✓Product Development Reports

✓ Computer systems

✓Sewage & Refuse

How to inspect API facility?

- We have not talked about areas which are very similar to Drug Product Inspection are :

✓ Some aspects Of Quality Management System like-

- Complaints handling
- OOS handling
- Change Controls
- Deviations Controls
- Recalls
- CAPAs
- Internal Audits (Self Inspection)

How to inspect API facility?

- In case API is intended to be processed further to render it Sterile , inspection approach will be very similar to Injectable drug products.

- Main guidelines which may be followed-
  - Annexure 1 to EU GMP guideline-Manufacture of Sterile Products
  - FDA's Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practices
  - FDA's Guide to Inspections of Lyophilization of Parenteral
  - FDA's CPGM 7356.002A –Sterile Drug Process Inspections
  - PICS recommendations on Validation of Aseptic Processes
  - WHO's Annex 6 – GMP for sterile pharmaceutical products

How to inspect API facility?

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❑**Guidelines which are useful while inspecting API facilities:**

- ICH guideline Q7-GMP guide for API. (Adopted in EU as Eudralex Vol 4 , Part II –Basic requirements for active substances……)
- ICH Q7 Q & As –GMP guide for API
- ICH guideline Q11 -Development and Manufacture of Drug Substances. (Adopted in EU as –EMA/CHMP/ICH/425213/2011)
- ICH Q11 Q & A- Development and Manufacture of Drug Substances
- ICH guideline on Impurities- Q3A,Q3C, Q3D
- ICH guideline on Stability- Q1A,Q1B, Q1D, Q1E
- ICH guideline M7 – Assessment & Control of DNA reactive (Mutagenic Impurities(Adopted in EU as EMA/CHMP/ICH/83812/2013)
- EMA's guideline on setting health based exposure limits(HBEL)……

How to inspect API facility?

❑**Guidelines which are useful while inspecting API facilities**

(Continued):

- EMA's Q & A on implementation of risk based prevention of cross contamination in production & guideline on HBEL……..
- APIC –"How to do" Document on interpretation of ICH Q7 guide
- APIC -guidance on aspects of cleaning validation of API plants
- ICH guideline Q2- Validation Analytical Procedures
- ICH guidelineQ9- Quality Risk Management
- ICH guideline Q10- Pharmaceutical Quality System
- FDA's Inspection Guidelines on Bulk Pharmaceutical Chemicals
- FDA's guideline on Pharmaceutical QC Laboratories
- FDA's guide to inspection high purity water systems

THANK YOU