

Unit 1: Process Chemistry

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Pharmaceutical Process Chemistry, subject code MPC204T, is a core Semester 2 subject of M.Pharm Pharmaceutical Chemistry. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. This subject is about what happens to a synthesis after it works in a flask. Process chemistry is often described as scale up: taking reactions from the small quantities created in the research laboratory to the larger quantities needed for further testing, and then to the still larger quantities required for commercial production. The goal of a process chemist is to develop synthetic routes that are safe, cost effective, environmentally friendly and efficient, and this course teaches how that is done for active pharmaceutical ingredients (APIs) and new chemical entities. Unit 1 covers process chemistry itself: synthetic strategy, the stages of scale up from bench to pilot to large scale, in process control and validation, case studies of API scale up, and impurities, including genotoxic impurities. Unit 2 covers the unit operations: extraction, filtration, distillation, evaporation and crystallization, finishing with polymorphs, hydrates, solvates and amorphous APIs. Units 3 and 4 cover the unit processes: nitration, halogenation and oxidation, then reduction, fermentation production of antibiotics, vitamins and statins, and reaction progress kinetic analysis with route selection and reagent families. Unit 5 is industrial safety: safety data sheets, hazard labels and protective equipment, fire, the OHSAS 18001 and ISO 14001 standards, and effluent management. A student who completes this subject should be able to explain why a reaction that is trivial at gram scale can be dangerous at tonne scale, and read a process the way a plant will run it.

1.1 What process chemistry is

A medicinal chemist and a process chemist look at the same molecule with different questions. The medicinal chemist asks: can it be made, and does it work? The process chemist asks: can it be made the same way, safely, batch after batch, at a cost the market can bear, in a plant that exists, with waste the law allows, and at a purity a regulator will accept? Process chemistry is the discipline that answers the second set of questions. Its raw material is a discovery route, usually designed to make many analogues quickly, with chromatography between steps and yields that were good enough for a pharmacology vial. Its product is a manufacturing process: a defined sequence of reactions and operations, with specified raw materials, quantities, temperatures, times, controls and acceptance criteria, that a production team can execute repeatedly.

Three features define the discipline. First, **scale changes physics**. A reaction that releases heat gently in a 100 millilitre flask releases the same heat per gram in a 4,000 litre reactor, but the reactor has far less surface area per unit volume to remove it through, so the same chemistry can run away at scale while behaving politely in the laboratory. Second, **economics are unforgiving**. A step that costs a few rupees of reagent per gram in research can decide whether a drug is commercially viable when the annual demand is measured in tonnes. Third, **quality is built, not tested in**. The API that reaches a patient must meet its specification for identity, purity and physical form every time, so the process, not the final analysis alone, is what guarantees quality. The syllabus scope states the goal plainly: routes that are safe, cost effective, environmentally friendly and efficient.

1.2 Synthetic strategy: choosing the route the plant will run

Synthetic strategy in process chemistry starts from the target and works backwards, as in retrosynthesis, but every disconnection is judged by manufacturing criteria as well as chemical ones.

- **Step count and convergency.** Every step costs time, solvent, labour and yield. A linear sequence of eight steps at 80 percent yield each delivers about 17 percent overall; a convergent route that builds two halves in parallel and joins them late loses far less material when one branch fails, and the longest linear sequence, not the total step count, sets the yield mathematics. Process chemists therefore favour convergent routes and fight to delete steps.
- **Starting material strategy.** A good process starts from cheap, commercially available materials with assured supply, ideally materials made at scale for other purposes. A route that begins from an obscure intermediate merely moves the problem upstream.
- **Protecting group economy.** Protecting groups add two steps each (on and off) and generate waste. Routes that exploit the molecule's own reactivity differences, or choose bond constructions that need no protection, are preferred.
- **Telescoping.** Several steps run in one vessel without isolating intermediates, using the output solution of one step as the input of the next. Telescoping saves time, solvent and handling losses, and is one of the clearest marks of a mature process.
- **Robustness.** The chosen chemistry must work within a forgiving range of temperature, charge quantity and raw material quality, because a plant cannot hold research laboratory tolerances. A route that only works in a narrow window is a route waiting to fail validation.
- **Freedom to operate and supply.** Patented steps, single source reagents and materials with hazardous transport classifications are all strategic risks that strategy must weigh.

1.3 The stages of scale up: bench, pilot and large scale

STAGES OF SCALE UP

Bench scale (laboratory)

gram quantities; route scouting and optimisation;
reaction calorimetry and hazard screening;
analytical methods developed alongside

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Pilot scale (pilot plant / kilo laboratory)

kilogram quantities; the process, not just the chemistry;
equipment trains rehearsed; engineering data collected;
material made for toxicology and early clinical supply;
safety and environmental behaviour measured at size

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Large scale (commercial plant)

hundreds of kilograms to tonnes; the validated process;
fixed batch records, in process controls, defined ranges;
material for the market, batch after batch

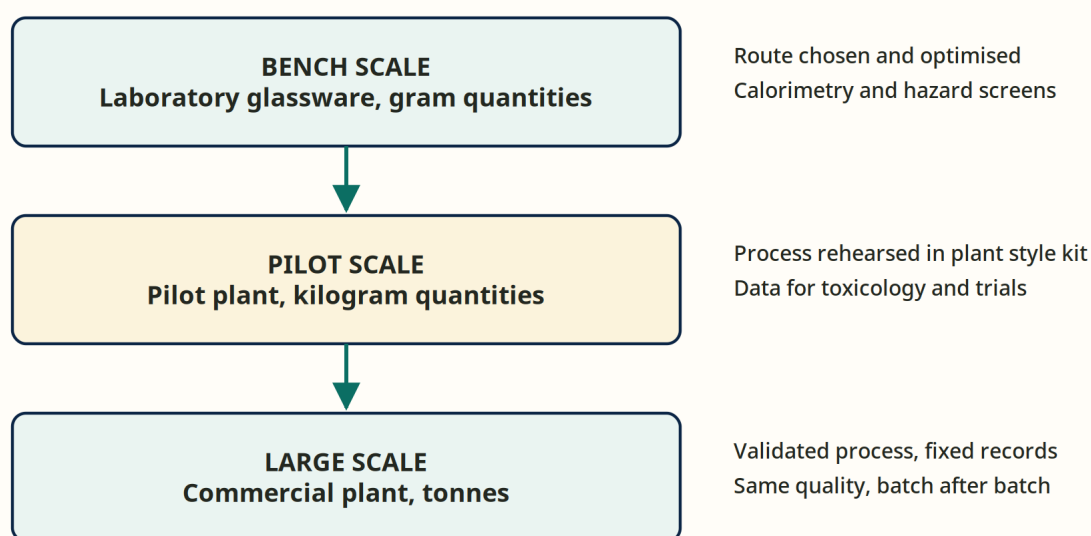
Bench scale is where the route is chosen and each step optimised, typically at gram scale in ordinary laboratory glassware. The work is chemical: yields, impurity profiles, solvent and reagent choice, and the first safety screens. Thermal hazard screening belongs here, because small scale calorimetry (differential scanning calorimetry of reactants and products, and reaction calorimetry of the process) tells the chemist how much heat a step releases, and how fast, before anyone runs it big.

Pilot scale translates chemistry into process. In a pilot plant or kilo laboratory, reactions run in jacketed vessels of tens to hundreds of litres, with plant style agitation, controlled additions and real work up operations: quenches, phase separations, distillations, filtrations and drying in equipment that behaves like

the factory's. New phenomena appear that the bench hides: additions take minutes to hours instead of seconds, so local excesses and hot spots occur; mixing times lengthen; emulsions form in extractions; filter cakes wash slowly; and the addition controlled nature of exothermic steps reveals itself. Pilot campaigns also manufacture the kilogram quantities of API needed for toxicology studies and early clinical trials.

Large scale is commercial manufacture in vessels of thousands of litres. The process is fixed in master batch records: specified charges, temperatures, times, sampling points and acceptance ranges, executed by operators who did not develop it. The purpose of the earlier stages is to make this stage boring: every variable that matters has been identified, ranged and controlled before the first commercial batch.

Stages of scale up: bench, pilot, large scale



Each stage answers the questions the next stage cannot afford to discover

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Figure: The three stages of scale up: each stage is larger, more formal and more expensive to be wrong in, so each must answer its questions before the next begins.

1.4 Why scale up is not just "more of the same"

The recurring examination theme of this unit is that scale changes behaviour, and four effects account for most of it.

- **Heat transfer.** Heat generation scales with volume; heat removal scales with surface area. Doubling vessel diameter multiplies volume by eight and surface area only by four, so a strongly exothermic step (nitration is the syllabus example, Unit 3) can outrun its cooling at scale. The defences are dose controlled addition, so the reaction only proceeds as fast as reagent is fed; adequate cooling capacity with margin; and knowing, from calorimetry, the maximum temperature the reaction mass could reach if cooling failed.
- **Mixing and mass transfer.** A magnetic stirrer homogenises a flask in seconds; a large vessel takes minutes, and during those minutes the composition is not uniform. Fast reactions in poorly mixed vessels give local over reaction, by products and, for gas liquid reactions such as hydrogenation, rates limited by gas transfer rather than by chemistry.

- **Time.** Charging, heating, cooling, filtering and drying all take longer at scale. An intermediate that is stable for the thirty minutes a bench work up takes may degrade during the six hours a plant filtration takes, so stability of process streams over realistic hold times must be established during development.
- **Materials and safety inventory.** A laboratory incident involves grams; a plant incident involves the full batch. Quantities of flammable solvent, toxic reagent and accumulated energetic intermediate are inherently larger, which is why hazard assessment deepens at every stage and why Unit 5 of this course exists.

1.5 In process control

In process control (IPC) is the system of checks performed during manufacture, as opposed to testing the finished API at the end. Its logic is that a process discovered to be off course early can be corrected; a finished batch discovered to be off specification can only be rejected. Typical IPC elements are:

- **Reaction monitoring:** samples withdrawn at defined times and checked by thin layer chromatography, HPLC or another suitable method for disappearance of starting material, appearance of product and growth of key impurities, with a defined end point criterion before work up is allowed.
- **Physical checks:** temperature, pressure, pH, addition completion, distillation end points (for example solvent exchange until a volume or composition limit is reached), water content by Karl Fischer titration where a dry stream is critical.
- **Isolation checks:** mother liquor losses (product measured in the filtrate), wash effectiveness, drying end point by loss on drying.
- **Hold time and deviation control:** defined maximum hold times for process streams, and a formal deviation record whenever the process departs from its instructions, with an assessment of impact on quality.

IPC results are recorded in the batch record as the batch proceeds, making the record a contemporaneous account rather than a reconstruction. In modern practice IPC is the shop floor expression of the quality by design idea: control the process at the points where quality is decided, not only at the gate.

1.6 Validation of the large scale process

Validation is the documented evidence that the process, run as written, consistently produces API meeting its specification. Development establishes what the process can do; validation proves it does so under routine conditions. The classical structure, taught across process chemistry and pharmaceutical quality courses, is:

- 1 **Define the process and its critical parameters.** From development and pilot work, identify the critical process parameters (temperatures, charges, times, pH values, solvent qualities) whose variation affects critical quality attributes of the API (assay, impurity levels, polymorphic form, particle size, residual solvents).
- 2 **Demonstrate consistency at scale.** The process is executed at commercial scale under the master batch record, conventionally over consecutive batches (the long standing industry convention is three consecutive successful batches), with full IPC and finished testing on each.
- 3 **Show the output meets specification every time.** Assay, individual and total impurities, residual solvents, physical form and other specification tests must pass on every validation batch, with impurity profiles comparable to the development and clinical batches, so that the commercial material is the same material whose safety was established.

- 4 **Document and lock.** Deviations during validation are investigated and explained; the validated state is then maintained by change control, so any later alteration to raw materials, equipment, parameters or site triggers an assessment of whether revalidation is needed.

Validation is why the pilot stage matters so much: a process that is merely possible cannot be validated, only a process that is robust, with proven acceptable ranges around each set point.

1.7 Case study: what scale up case studies teach, the ibuprofen routes

The syllabus asks for case studies of scale up processes of APIs without naming them; the example used across the process chemistry literature, and the one taught here, is ibuprofen, because its two industrial routes show exactly what process development is for. These are the standard teaching examples, not processes named in the syllabus.

The original **Boots route** (1960s) built ibuprofen in six steps from isobutylbenzene, beginning with a Friedel Crafts acylation and passing through a Darzens reaction and a hydrolysis, decarboxylation sequence. It worked, and supplied the drug for decades, but its atom economy was poor (about 40 percent of the reactant mass ended in the product on the commonly quoted calculation), it used stoichiometric aluminium chloride with its aqueous work up and waste, and six isolations meant six opportunities for loss.

The **BHC route** (Boots Hoechst Celanese, commercialised in the 1990s) reaches the same molecule in three steps: Friedel Crafts acylation of isobutylbenzene with acetic anhydride catalysed by hydrogen fluoride, which serves as both catalyst and solvent and is recovered and recycled; catalytic hydrogenation of the ketone to the alcohol; and palladium catalysed carbonylation of the alcohol to the acid. On the standard published comparison its atom economy is about 77 percent, rising toward 99 percent when the recovered acetic acid by product is counted, and it won a United States Presidential Green Chemistry Challenge Award in 1997. The teaching points are the syllabus points: fewer steps, catalysis in place of stoichiometric reagents, recovery designed in, and waste prevented rather than treated. A case study answer follows this pattern: what the research route was, what limited it at scale, and what the process route changed.

1.8 Impurities in APIs: types and sources

An impurity is any component of the API that is not the API itself. Controlling impurities is a central duty of process chemistry because the clinical safety of a drug is established on material of a particular purity; commercial material must match it. Sources and types organise as follows.

Impurity type	Typical source in the process
Unreacted starting materials	Incomplete conversion; carried through when a step's end point is missed
Intermediates	Partial reaction, or an intermediate from an earlier step not purged at isolation
By products of the main reaction	Competing pathways: over reaction, under reaction, regioisomers, elimination and rearrangement products
Products of side reactions with reagents and solvents	Solvent or reagent adducts, for example ester formation between an acid API and an alcoholic solvent
Degradation products	Hydrolysis, oxidation, heat or light damage during processing, holding or storage
Reagent and catalyst residues	Metal catalysts (palladium, nickel), acids, bases and their salts incompletely removed at work up
Residual solvents	Solvents retained in the crystal or dried cake; controlled to ICH Q3C limits
Enantiomeric impurity	The unwanted enantiomer from a non selective step or partial racemisation

Impurity type	Typical source in the process
Inorganic impurities	Salts, filter aids, charcoal fines, water borne material

Control is exercised at three levels. **Prevention** is process design: order of addition, temperature and stoichiometry chosen so the impurity forms minimally. **Purging** is the deliberate removal at crystallisation, washing, extraction or charcoal treatment steps, ideally demonstrated by spiking studies showing how much of an impurity each operation rejects. **Specification** is the final guard: the API specification sets limits, within the ICH Q3A framework, under which impurities are reported (above 0.05 percent for a maximum daily dose up to 2 grams), identified (above 0.10 percent or 1 milligram per day intake, whichever is lower) and qualified, meaning shown to be safe at that level (above 0.15 percent or 1 milligram per day, whichever is lower). The process chemist's aim is a process whose normal output sits comfortably below all three thresholds without heroics.

Where the impurities in an API come from

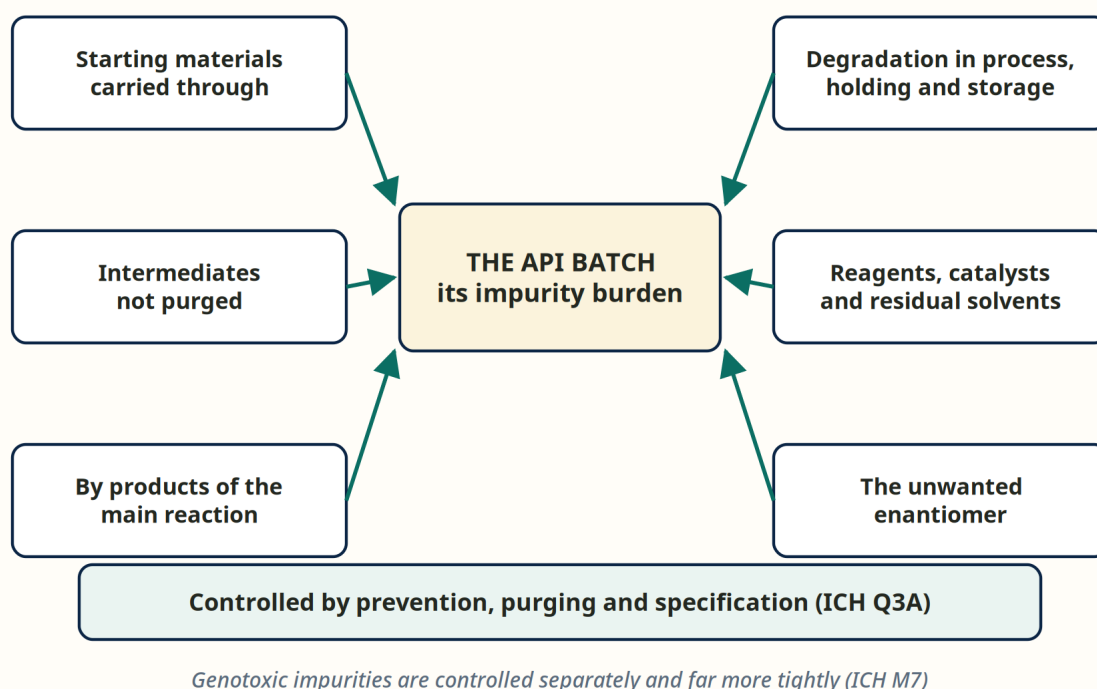


Figure: Every impurity in the API arrived from somewhere in the process; control is exercised by prevention, by purging at isolation steps, and finally by specification.

1.9 Genotoxic impurities

Genotoxic impurities are impurities that can damage DNA and are therefore controlled far more tightly than ordinary impurities, because for direct DNA reactive mutagens no safe threshold is assumed. The subject entered routine practice through cases in which sulfonate ester impurities, formed when sulfonic acids met alcoholic solvents, were found in marketed products, and it is now governed by ICH M7. Key ideas:

- **Structural alerts.** Certain chemical features flag a compound as potentially DNA reactive: alkyl halides, sulfonate esters, epoxides, hydrazines, aromatic amines and nitro compounds, and nitrosamines among others. An impurity carrying an alert is assessed, not automatically condemned: data, computation and, where needed, a bacterial mutagenicity (Ames) test decide its class.

- **The threshold of toxicological concern (TTC).** For a mutagenic impurity without compound specific data, the default acceptable intake under ICH M7 is 1.5 micrograms per day for lifetime exposure, with higher staged limits permitted for short treatment durations. Translating an intake in micrograms into a concentration limit in parts per million for a given daily dose is a routine calculation, and it routinely lands far below the ordinary 0.10 percent identification threshold, which is why genotoxic impurities need dedicated analytical methods and dedicated control strategies.
- **Control by process design.** The standard strategies are to avoid forming the impurity (choose a different reagent or solvent pairing, for example not holding a sulfonic acid in an alcohol), to introduce the alerting reagent early and demonstrate purge through later steps, to test at an intermediate stage rather than in the API, or to test the API with a suitably sensitive method. The nitrosamine findings in sartan medicines from 2018 onwards, in which nitrite and vulnerable amine chemistry combined in some processes, made the same lesson public: genotoxic impurity control begins at route selection, not at the specification page.

1.10 Unit 1 summary

Question the unit answers	Core answer
What is process chemistry?	Developing syntheses into safe, economical, validated manufacturing processes for APIs
What changes with scale?	Heat removal per volume falls, mixing slows, operations lengthen, inventories grow
What does IPC do?	Detects drift during the batch, while correction is still possible
What does validation prove?	That the written process, run routinely, consistently meets specification
Where do impurities come from?	Starting materials, intermediates, by products, degradation, reagents, solvents
Why are genotoxic impurities special?	DNA reactive, no assumed safe threshold, TTC based limits in micrograms per day

Unit 2 now looks at the physical operations that every process uses to move and purify its material.

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