Introduction to process chemistry in the pharmaceutical industry

Process chemistry is arguably the area where most of the effort towards incorporating green chemistry has been achieved to date. Process chemistry involves development of practical, safe and cost effective processes for the synthesis of compounds selected to progress from research/discovery to a larger scale. Within the pharmaceutical industry synthetic routes developed within medicinal chemistry often have to be completely redesigned by process chemists, and this is in part due to their differing requirements. The differences between medicinal and process chemistry and the multitude of factors that need to be taken into consideration when scaling up a chemical process are discussed in this module.

Learning Objectives

By the end of this module you should:

- Understand the differences and synergies between medicinal and process chemistry;
- Understand the factors affecting the scaling up of processes;
- Be able to describe the journey from research to process chemistry.

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Process chemistry vs. medicinal chemistry

For medicinal chemists diversity and flexibility of a route is important. They synthesise a wide range of analogues of a lead compound on a small scale (ca. 20mg) for testing in order to increase activity, reduce side effects and to produce an API that may be easily and efficiently administered to the patient. For this the compound must have the right properties in terms of activity, toxicity, solubility, pharmacokinetics and pharmacodynamics.

In contrast, process chemistry involves development of practical, safe and cost effective processes for the synthesis of compounds on a larger scale (kg to several tonnes) that have been selected to progress from medicinal chemistry. They generally therefore work on a single target molecule and define the best route to that target. **Figure 1** below summarises the key stages in process chemistry for the development of an active pharmaceutical ingredient (API).

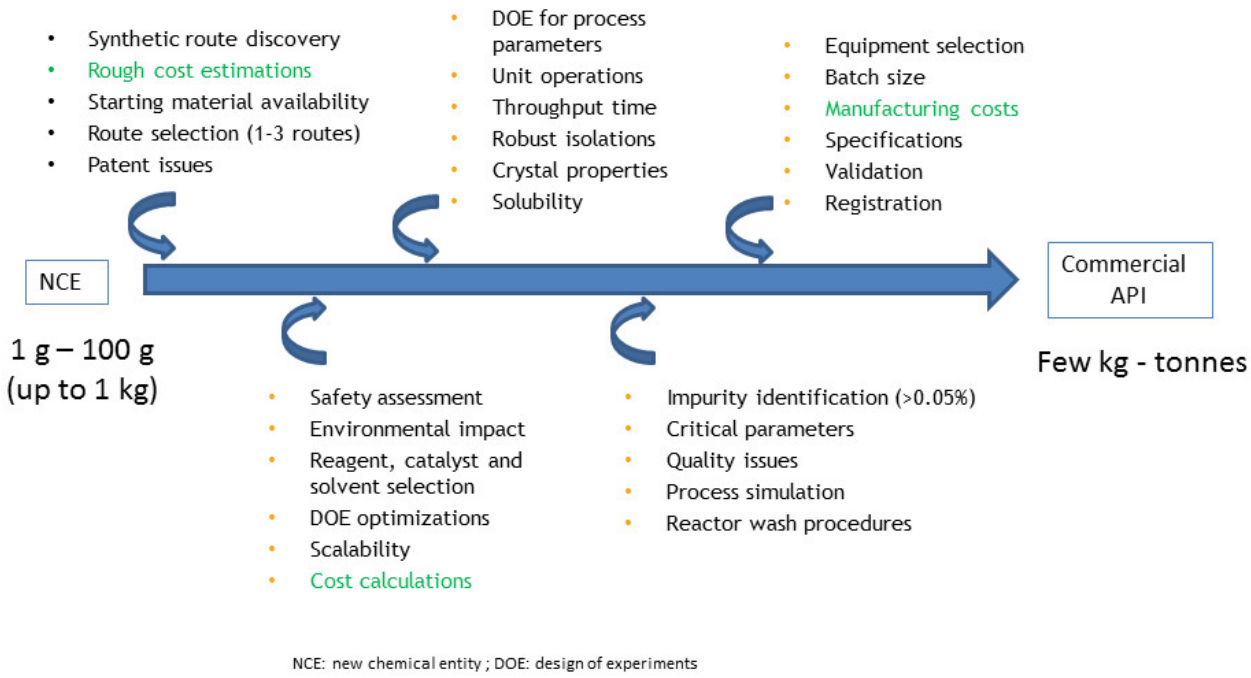

Figure 1: ***The key stages in process chemistry for the development of an active pharmaceutical ingredient***

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Transcript

Coming again to the borderline between medicinal or chemist and process chemist, the medicinal chemist looks to the physical or chemical parameters of your molecule.

It looks to the molecular weight; it should not be too high you have to have a certain pKa, you should have a certain logD value and you look to the polar surface area because depending on the polar surface area, it may not be able to enter the brain.

And to know the 3D structure of your molecule because this 3D structure, in the end determines how it is your molecule is interacting with the protein.

Important to know! And, of course, you know a little bit about patenting because it should be a new molecule, because if it has been described before, bad luck! It's not an invention.

And you, of course, know about toxicological effects, so there are some functional groups you don't like to have that much.

So nitro, maybe not the best.

Also some phenols, maybe not that great to have.

So that's something you have to have in your mind when you design your molecule and when you actually prepare it.

And then you get the answer, you get the answer from your biological colleagues telling you 'well you have an active molecule but, sorry to say, it's not entering the cell so go again and get some new stuff' so that's actually what's ongoing here, so what is actually the dynamic of the molecules? So what is actually the effect of the drug on the protein level, on the cellular level, on the body? Or, what is the body actually doing to that? But we have something in common with my colleagues in process chemistry.

We are still synthetic chemist.

If you can see this, quite a bit of difference in the keywords in here.

And first time I was asked to do the presentation about the difference, I felt like I have to compare apples and oranges.

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They're both round, that's it.

But we're looking at different things, the price of the starting material, safety, of course, waste does cost quite a bit of money and if it's aqueous waste do we have to burn it? Or can we just put it in the water waste treatment facilities? And, of course, the campaign times, throughput times.

Sometimes your reaction is one hour but the isolation procedure and the reactor wash, that's 12 hours.

So that's high, this is a very important factor.

also the batch size because of the validations you have to have an idea what is your true batch size for the API, for the annual requirement for the API.

Because once you lock this, you can't change it, because after that you have to revalidate and re-register your process again.

And of course the main issue is you've got to look at the the final API.

what is it? Is it crystalline you want or amorphous? What is the polymorph you want? Because of course we saw the presentation from where they might be over 10 different polymorphs for one compound.

And also the solvents and of course the particle size are what we're looking.

And all of these impact, eventually, the price of the API.

So I've prepared on one slide what is process chemistry.

Of course we have the winds nice lecture but will.

Case study

In this video Esa Kumpulainen describes a literature example of a medicinal chemistry versus a process chemistry route to a target compound.

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Here's an example of a typical Med Chem route.

Since I can't use any structures from my company, I went to one of my favorite papers, OPRD, and found a Japanese example and the reason why I can kind of like this the molecule looks like an API.

It's definitely a pharma target.

So what we're looking here is a very typical starting material for a Medicinal Chemist; extremely expensive and the source article says that they paid this money for it, but i took a price from Sigma-Aldrich because generally we buy everything from Sigma-Aldrich because that's the fastest way of getting material.

And in here you can see fluorine which is required for the later stages.

We use a lot of chromatographic steps and this is 'no, no' for the production scale because you can't do that.

Well, there are probably x samples of kilogram chromatography in the world but eventually, you can't do that.

Then these hazardous chemicals which might be toxic and even recently one of our process chemists told one of the med chemists that 'you can't use sodium azide, invent something new, redesign your route'.

And eventually we're looking at, kind of total 10 steps and we get the material done.

And I marked down the steps that is the expanding so we're getting the medicinal chemistry idea of diversity.

You need the fluorine because you want to be sure that at the later stage that it works every single time.

Putting some other thing you can make diversity.

Building more diversity and an amide coupling which is used by everybody still and we're struggling; everybody's struggling with it and it builds more diversity so you get much more diverse kind, a lot more, a huge amount of APIs, or NCs in this case.

Well, what happens when a Process Chemist takes over? So starting material? A lot cheaper.

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I found an even cheaper price from a database than they're claim in their original article.

And the biggest issue you can see the precipitation, precipitation, active extraction, evaporation, so they evaporate to dry and that goes to the next step.

And you see no chromatography and although this particular example starts with the kilogram, it ends up into 200 kilograms, you can see the scale up is there already.

So you can probably scale this up to a multi kilogram, multi-ton operation, but I don't know what happened to this particular API.

From Meiji Seika Kasha and that's the other code, I think it's a teacher or the company like that.

But there was also some issues in here.

Of course they use a genotoxic impurity in this case, but the azide is also gone so there's an amination, a transfer amination or hydrogen amination in here.

And of course in one case we have a transesterification but it carries to the next process and they can still isolate this product in high yield.

This is a typical difference between a Med Chem and a Process Chem..

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Application of the SELECT criteria

In this video Wim Aelterman provides a brief summary of the SELECT criteria, before going on to describe each of them in more detail in the following sections.

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Safety

Safety is the number one criteria for research and development. In this video Wim Aelterman describes safety risks including thermal and reactive hazards, and toxicity, which become increasingly important as processes are scaled up.

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Transcript

So the first criterion is Safety.

No coincidence that this is really the number one criteria because we cannot afford to develop a process which on large scales is failing and that there is, for example, an explosion, where potentially people can die and that also there can be a complete destruction of the commercial supply chain, where also it could mean that patients do no longer have access to the medicine at a certain moment.

There are at least two types of, or two categories of hazards.

The first one is thermal and reactive hazards, has to do with the property of the reaction itself, to avoid that there is a thermal runaway we have the reaction mixture is getting to a temperature above which it is no longer stable.

Second, on the large scale if there is a reaction where gas is evolving.

It's completely different than on lab scale.

If you are doing, for example, a BOC de-protection on small-scale, you do not worry about the fact that you are generating iso-butene, but on large scale we are talking about

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potentially significant volumes of iso-butene during the BOC de-protection.

That's just one example, but at de-methylation with HBr where you are generating methyl bromide, you might not consider that in a lab environment but on large scale it's an important attention point.

Certainly potential explosives, to be careful when handling these on large scale.

Some of the reagents we are using are really corrosive, so on the long term we have to make sure that we can run, we can keep our equipment in a decent state.

So we have to select the right equipment and protect it as much as possible.

And also pyrophoric material, pyrophoric reagents, need special attention; for example, for storage, but also for dosing, for neutralization after the reaction .

The second category are the toxic hazards, where the general principle is that first of all we try to avoid them.

Avoid them by not using them, by using other reagents which are less toxic.

If there is no real alternative, we try to reduce them; reduce the amount and after that we try to control that.

On the one hand by containment and by engineering the process and the equipment, such that it's in a closed environment.

And it's really needing also to protect the workers who has to handle these reagents on a large scale.

And there's a difference between acute and chronic toxicity as you are aware of, for some of them you will observe it immediately that there's something wrong, for others you only see the effect after a long time.

General principle is: If you can't scale it safely, don't scale it at all.

A little bit of foam in the lab can be funny, not a problem, but some foaming on large scale, uncontrolled, and it can be, potentially, very toxic what's coming out of the reactor here.

I'm sure you agree with me that you don't want to to see that..

Environmental

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The pharmaceutical industry follows the environmental ideals of preventing, minimising and rendering harmless any reagents used and wastes generated from processes. Different metrics are utilised within the industry to track and minimise environmental impact. Steps taken to improve environmental credentials for a process are considered by Wim Aelterman in this video.

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Legal

In this video Wim Aelterman describes legal considerations including regulation of substances by governments, environmental legislation and patent law.

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Economic

In this video Wim Aelterman discusses economic considerations.

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Control

Quality control is essential for commercial production of an API (active pharmaceutical ingredient). Selectivity, stability, purification, registration and validation of processes, product specifications and genotoxic impurities all need to be considered to ensure quality is suitable for market. In this video Wim Aelterman discusses these parameters in more detail.

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When you are finally going into commercial production, you have to guarantee a constant quality.

So in order to do that the selectivity of the reactions has to be the same, it has to be a very robust process.

You also have to understand the chemical and physical stability of, for example, the intermediates of the synthesis, how long can you store them? That's important.

Do you need a refrigerated conditions to store them? This is certainly the case for the active itself, so specific stability tests are being set up running over 24-36 months and depending on where the component will be marketed.

These are running on the different conditions; at 30 degrees, at 40 degrees, different relative humidity as well, 75 percent relative humidity.

So that's part of the control strategy, making sure that the active really can be stored under stable conditions where we don't see degradence.

Another aspect; that to guarantee that control quality we built in a number of purification points in the synthesis.

Certainly the final step itself but it could be also intermediate purification points.

Part of the control strategy is also that when we submit a file to authorities the steps are, what we call, post the registered starting materials are described in full detail, including parameters.

For example settings of temperatures, stirring times, and obviously we cannot deviate from that so it's registered in the filing.

Every time we reproduce a new batch we have to stay within these filed limits so that's part of the control strategy.

The processes before they are marketed are also validated, so you run a number of batches within preset criteria that, in advance, you say that these are the criteria we want to meet, these are the settings we will use and we will run a number of batches and they have them to obtain a certain preset quality as well.

The final product itself, the API, is controlled not only for organic impurities but also, for example residual solvents that have specific guidelines, what we call ICH guidelines which have been met for every API and also, for example, for metals, specifically heavy metals, there are specific guidelines that we have to meet.

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There have been several initiatives and some of you might have heard about Quality by Design so it's really to understand the processes that are being used, for example, design of experiments issues there to check parameter combinations.

If you have a certain time, or a certain temperature are we still meeting the expected quality? And we are also defining normal operating ranges and proven acceptable ranges.

So the proven acceptable ranges, this means if you go beyond that, that you are almost at the edge of failure of your process.

And obviously, the acceptable ranges are more broader than the normal operating ranges.

So what are the typical levels that are allowed in the final product? It depends on the on the dosage, but let's say for most products which are, at worst, less than 2 grams a day, you can specify impurities.

If you have demonstrated with specific toxicity that these levels are allowed, but typically we have to report every level that's higher than 0.05% and we have to identify the structure of every compound that's present above 0.10% and active itself.

I was referring to genotoxic impurities, they have to meet different levels, so for commercial products that's 1.5 micrograms a day which is, for example, if you have two x 750 milligrams tablets, one and a half gram a day, it means that the specific impurities have to be below 1 ppm for that product.

This is, I would say, that concern has been raised and increasing over the past six, seven years and certainly led to the fact that quite a number of, for example, sensitive analytical methods have to be developed for our APIs just to make sure that we don't have these potentially genotoxic impurities in there.

For example if you are making an HCl salt in ethanol, you might not be aware of that, but you can be sure that there will be ppm levels of ethyl chloride which is a genotoxic compound, if you have not very carefully designed your process.

So it's an additional criterion, I would say.

It has certainly generated some additional development work, analytical work at to make sure that we can meet these very low levels..

Throughput

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In this video Wim Aelterman discusses throughput.

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Finally, the last criteria which is important is the Throughput.

Making sure that we can produce enough within a given time, where chemical yields plays an important role, trying to work as concentrated as possible; if you have one very diluted step in the middle of synthesis this can really be a bottleneck.

So, for example, certain types of chemistry like metathesis, ring-closing metathesis, which is in most cases run at very diluted conditions.

If you have to perform that several steps before the API this might be real bottleneck and not allow you to make a sufficient volume.

What's quite often used is a telescoping of reactions, meaning you work in the same solvent for a number of consecutive steps which is really improving throughput because you don't need to isolate intermediates, don't need to filter or centrifugate them, you don't need to dry them as you don't need to bring them again or dissolve them again for the next step so that's one way to really improve throughput..

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Summary and further reading

Comparison between medicinal and process chemistry highlights some of the key differences between small scale research and scale up moving towards commercial production. Upon scaling up from laboratory research to larger scale production there are a number of factors that need to be taken into consideration. **Table 1** summarises the SELECT criteria along with the associated considerations and potential issues.

Criteria	Sub-criteria	Examples of Potential Issues
Safety	Process safety	Explosions
	Exposure to harmful substances	Carcinogens, sensitisers
Environmental	Wasted resources	Quantity & variety of solvents
	Substances harmful to the environment	Aquatic toxins, ozone depleters
Legal	Infringement of Intellectual Property	Competitor patenting key intermediate
	Regulation of reagents and intermediates	
Economic	Meeting Cost of Good (profit margin)	Long synthesis or expensive starting materials
	Investment costs (equipment)	
Control	Control of quality	Meeting specifications/ GMP
	Control of physical/chemical parameters	
Throughput	Time scale of manufacture	Long synthetic route
	Availability of starting materials	Rare natural products

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Table 1: The SELECT criteria with associated potential issues.

Recommended reading:

- M. Butters, D. Catterick, A. Craig, A. Curzons, D. Dale, A. Gillmore, S. P. Green, I. Marziano, J. - P. Sherlock and W. White, Critical Assessment of Pharmaceutical ProcessesA Rationale for Changing the Synthetic Route, *Chem. Rev.*, 2006, **106**, 3002-3027.
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- P. J. Dunn, The importance of Green Chemistry in Process Research and Development, *Chem. Soc. Rev.*, 2012, **41**, 1452-1461.
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Multiple choice questions

1. Which of the following are similarities between medicinal chemistry and process chemistry?
    1. Both are working towards developing a finished product
    2. Both are working at the same development stage on the timeline
    3. Both require analysis and verification of process
    4. Both require knowledge of chemical synthesis
    5. Both work on the same number of molecules
    6. Both have

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