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PROCESS SCALE-UP AND ASSESSMENT

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20.1 INTRODUCTION

One of the key roles of chemical engineers in drug substance process development is transforming an active pharmaceutical ingredient (API) synthesis route into a scalable commercial process. In this chapter, we present an approach to process assessment and scale-up focused on risks to safety, quality, and business that takes into consideration the product's stage of development and the magnitude of scale-up. Emphasis is placed on understanding common unit operations' scale-up factors, and use of this knowledge in the assessment and definition of a development strategy.

The initial chemical synthesis of a small molecule active pharmaceutical ingredient is typically developed by an exploratory or discovery chemistry group. The goal of the initial synthesis is to quickly enable production of milligrams to grams of the API to support exploratory studies and to confirm the biological activity of the molecule. This initial route is designed to be divergent and allow access to a variety of targets and is not designed for further scale-up to kilogram scale, much less to a manufacturing process. It is the role of process chemists to design a synthesis that can be developed into a scalable process to deliver sufficient API quantity and quality to support clinical, toxicology assessment, and downstream formulations. It is a collaboration of process chemical engineers with the process chemists that shapes the synthesis from a procedure to a plant-scale process.

20.1.1 Phases of Development

The focus of the chemical engineer in transforming a synthesis into a scalable process changes as the compound goes through the various stages of development. The evolution of the synthesis route is tied to the clinical timeline. Table 20.1 provides a simplified overview of the evolution of the synthesis and product requirements as the stage of development progresses.

In reality, the progression of development is likely not as clearly defined, and overlap of these categories will occur, depending on the compound's potency, synthesis and molecular complexity, the therapeutic class of the compound, and the infrastructure and organization of the Process R&D group. However, the process development goals can be generally delineated within these milestones in terms of the magnitude of scale-up, and the process safety, business, and quality risks. This, in turn, guides the allocation of engineering resources and determines the level of risk assessment needed.

20.1.1.1 Early Development In early development, the synthesis milestone is the selection of an appropriate route for the initial scale-up. The key considerations are process safety, chemical hygiene, number of synthetic steps, availability of reagents, raw materials, and intermediates, and ability of the synthesis to address API quality. The top process assessment priority is to identify hazardous reactions and reagents, and to evaluate safe operating limits and material exposure limits. Altering the reagents and conditions and/or developing engineering controls to ensure safe operation are the main engineering foci. The secondary process assessment priority is to meet targeted process development goals. These goals would be (1) to obtain sufficient process knowledge to support at-scale operations (first-order scale effects, stability over duration of unit

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TABLE 20.1 Process Research and Development Requirements During Stages of Development [1,2]

Stage of Development	Discovery	Early Development	Full Development	Launch
Clinical stage	IND toxicology	Phase I	Phase II	Phase III/launch
Type of synthesis	Expedient	Practical	Efficient	Optimal
Synthesis milestone	Enabling synthesis	Route (intermediates) selected	Sequence of unit operations finalized	Process parameter ranges finalized
Amount of compound	10 mg–10 g	100 g–10 kg	10–100 kg	>100 kg
Site for preparation	Laboratory	Kilo laboratory	Pilot plant	Manufacturing plant
Number of batches	1–5	1–10	10–100	10–1000
Probability of success to next stage of development [3–6]	40–60%, preclinical to clinical	40–60%, phase I to phase II	40–60%, phase II to phase III	80–100%, phase III to NDA filing and launch

operations, heat/mass transfer, and hold points) and (2) understanding, but not optimization, of the process conditions (stoichiometry, temperature, concentration, filtration) to enable appropriate equipment usage. Process knowledge may be limited to single point information rather than a design range. The API product quality must meet an initial set of specifications, which may include form, purity, stability, and impurities.

At this stage of development, the probability of the molecule achieving success for a New Drug Application (NDA) is still low (<10%), and there is a high likelihood that the chemistry will not be used beyond this stage of development. Thus, fewer engineering resources will generally be allocated.

20.1.1.2 Full Development In this stage of development, the compound has demonstrated some key human safety milestones (phase I) and/or some evidence of clinical response or efficacy. A clinical timeline can be projected for the compound that will lead to a New Drug Application.

By this stage, the process chemists will have evaluated alternate synthetic routes and will have determined the desired sequence of intermediates. The development will focus on finalizing the chemistry and reagents and defining the API crystal form and powder attributes. The process scale-up assessment will continue to have strong process safety and quality focus. In addition, an evaluation of the business risks will guide the efforts to develop a robust, efficient, and economical manufacturing process. Key aspects to evaluate for this assessment include yield, cycle time, equipment usage, waste output, and need for analytical support such as in-process assays and process analytical technology.

At this phase of development, the probability of success for the molecule to be filed for approval has increased significantly. The optimized process must consistently meet the quality requirements at the pilot plant scale before the next stage of development.

20.1.1.3 Launch This stage of development will focus on the final process optimization and providing a full understanding of the chemistry, manufacturing, and controls (CMC) for the New Drug Application. Detailed information on process parameter ranges and fundamental understanding of the key unit operations (e.g., reactions, crystallizations) will be required to support the process validation at the manufacturing site and the submission of the NDA.

20.1.2 Process Safety and Risk Assessments

Risk is often defined as the combination of the probability and the severity of a harmful occurrence. Regulatory guidance to the pharmaceutical industry on evaluating risk is that the protection of the patients is of prime importance [7]. Protection of workers and maximizing business objectives are also key goals in assessing risk. Thus, the assessment of a chemical process must cover three key aspects: safety, product quality, and business parameters. Safety and quality risk assessments are inherent in all phases of development, while the emphasis on business risk assessment increases in the later stages of development. Process safety is tied to standards and regulations governed by government safety agencies and acceptable and appropriate product quality is guided by the various ICH (International Conference on Harmonization) guidelines for registration of pharmaceuticals for human use [8].

20.1.2.1 Process Safety Assessment Process safety assessment is one of the main chemical engineering concerns throughout process development. As Chapter 11 covers this topic in more depth, this chapter will briefly review some of the key elements of such an assessment and its impact on process scale-up.

For any scale-up, the first step is a review of process safety to (1) examine the reaction issues such as impact of chemical mixing, rate, sequence, and mode of charges, parameters for self-heat, potential gas evolution, corrosivity; (2) evaluate the thermal and chemical stability; and (3) evaluate the electrostatic and dust hazards. Issues raised in this review require identification of safe limits by understanding the mechanisms of the hazards, and an engineering evaluation to provide appropriate controls to meet such safe limits. This review is typically followed by a safety assessment against the

scale-up implementation plan. An example would be a Process Hazards Analysis (PHA) [9] that uses a standard methodology to evaluate potential process and equipment hazards that could cause the catastrophic release of hazardous materials or other significant safety impacts and ensures that appropriate safeguards are in place to prevent, detect, or mitigate these occurrences.

As an example, for a highly exothermic reaction, chemical engineers can (1) evaluate the equipment capabilities (i.e., heat transfer or mass transfer rates), (2) optimize the chemistry via reactants and reaction conditions (i.e., changing the mode, sequence, or rate of a reagent charge, which change the kinetic stoichiometry), and (3) adjust the process setup to mitigate the hazard (i.e., emergency quench vessel, addition of external heat exchanger to increase cooling).

20.1.2.2 Process Risk Assessment There are various goals in a process risk assessment, which may take many forms. Regulatory guidance sets the primary goal of a risk assessment as identification of issues resulting in drug product quality that adversely impacts the patient's health. For API synthesis, this means identifying the process parameters that can cause the drug substance to fail its critical quality attributes. Such critical quality attributes may include product potency, crystal form, impurity levels, and physical properties such as particle size distribution. Process issues that impact overall productivity, capacity, or process greenness are considered business risks, because they have little or no impact on the quality of the drug substance.

Some risk assessment goals are short term such as an evaluation to ensure that the chemistry is scalable in the proposed equipment. This usually involves having sufficient prior experience to maximize the probability of success to safely produce material of desired quality. There are also longer term risk assessment goals such as evaluating the process design and synthesis against the combination of desired safety, quality, and business criteria.

The risk management process may be informal, using relatively simple empirical tools such as flow charts, check lists, questionnaires, process mapping, and cause and effect diagrams to organize the data and facilitate decisions. Risk evaluation may also utilize formal processes and methodologies. Two recognized tools are listed as follows:

1. Failure mode evaluation and analysis (FMEA) [7] to score and quantify risks by identifying potential failure modes and the impact on product quality.
2. Kepner–Tregoe analysis [10,11] to provide a quantitative assessment of the synthesis, taking into consideration both quality and business risks.

Other tools, adapted from safety risk analysis, such as PHA, Hazard Operability Analysis (HAZOP), and Hazard Analysis and Critical Control Points (HAACP) [7], apply a failure analysis to meet set criteria of safety, product quality, and/or business deliverables. These approaches are particularly valuable when performing a systematic review of the processability and scalability of the chemistry for commercial manufacturing.

20.1.3 Manufacturing Considerations

The short-term focus of process scale-up and assessment is on glass plant or pilot plant processing; however, as a project moves through development, the focus will shift to address manufacturing scale concerns. There are a number of differences to consider when assessing the process for either the pilot plant or manufacturing scale-up. Some of these differences are generalized and tabulated in Table 20.2.

These differences can have significant implications for the process scale-up assessment. The flexibility and technical support in a pilot plant environment may allow equipment setups and tighter control of process parameters than is typical or possible in a manufacturing plant. These factors must be understood to design a robust commercial process.

20.2 DRIVERS FOR DEVELOPMENT/RISK ASSESSMENT

The process development strategy is defined by risk management across three main areas: safety, quality, and business. Both safety and quality are necessary attributes of a scalable synthesis at any phase of development. Therefore, at a minimum, there must be sufficient development to manage the risk to safety and quality. In the absence of safety and/or quality concerns, business considerations define the development strategy. The challenge is defining the level and timing of development work as projects transition from early

TABLE 20.2 Pilot Plant Versus Manufacturing Differences

Consideration	Pilot Plant Scale	Manufacturing Scale
Equipment size	50–4000 L	400–12,000 L
Operating hours	5 days ($\leq$24 h/day)	7 days (usually 24 h/day)
Technical support	Process engineer/ chemist	Plant engineer
Automation	Manual to fully automated	More likely automated
Analytical support	Short turnaround ($<$1 h)	Long turnaround
Equipment setup	• More likely to utilize unique equipment with flexible setup • Mostly sequential operations	• More likely to utilize only standardized equipment • More likely to have parallel operations

to full development. Throughout the stages of development, it will be impossible to understand and eliminate all the risks. The key is to eliminate enough risk to ensure that the differences upon scale-up do not impact the development goals.

By understanding the goal of the scale-up and performing an assessment against the goal, the development needs can be prioritized. In early development, the goal will include safety and quality aspects. While the business factors for process optimization are not key drivers, there are still scenarios to consider such optimization. These drivers will be based on the complexity of the synthesis route, the long-term synthesis strategy, the project timeline, and the facilities' constraints. Some examples of such drivers are outlined in Table 20.3. As the project moves forward through development, business goals will become a higher priority.

The initial process scale-up assessment is typically performed as a paper exercise guided by prior experience. Then, a laboratory assessment is usually necessary to evaluate unknown risks. Evaluation of such unknown risks can usually be performed in a few well-planned experiments. For example, the impact of processing time is typically unknown in early development and is highly likely to change as the process is scaled. During laboratory runs of the process, sampling at key points and aging the samples at the processing conditions will provide sufficient information about the process stability over the plant-scale time frame. Example 20.1 is given to illustrate an initial process assessment for an early development project. The impact of each unit operation on safety, quality, and business is evaluated (Table 20.4).

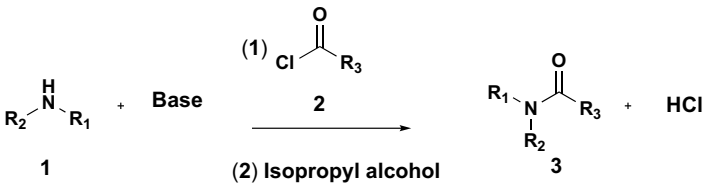
TABLE 20.3 Drivers for Development Outside of Safety/ Quality Issues in Early Development Programs

Issue	Driver for Development	Potential Development Activities
Length of synthesis	Availability of plant time to prepare	Alternate route development
Low yield in synthesis	the chemistry to meet API needs	Increased throughput by • higher yields • smaller maximum volume (V_{max}) • decreased cycle time
Sourcing of reagents	Key reagent not available in time for scale-up activities	Alternate route development Replacement of reagent
Intellectual property	Some key elements of synthesis under patent protection	Alternate route development to replace this element of synthesis

EXAMPLE 20.1

Process Description

1. Compound **1** is mixed with solvent and base, heated to 40°C, and aged for 1 h to activate the amide hydrogen (**1**) (Scheme 20.1).



2. The solution is then cooled to 0°C and excess acid chloride (**2**) is added, initiating the coupling reaction to form amide (**3**). The reaction is exothermic and the temperature must be maintained at $\leq$5°C.
3. The reaction is then quenched at $\leq$20°C by addition of isopropyl alcohol. The quench is exothermic. Several process impurities are formed during the reaction and quench, with impurity A found to be a suspected carcinogenic compound.
4. Compound **3** is then crystallized at 20°C by addition of an antisolvent. Impurity A cocrystallizes with compound **3**.
5. The slurry is then filtered, the wet cake is washed to remove impurity A, and solid compound **3** is dried under vacuum at 50°C.

In this assessment (Table 20.4), the initial activation is shown as low priority and the crystallization and stability are both shown as medium priority. In early development, the absence of information regarding the activation is not considered an issue since it is likely that the process will not deviate significantly from the lab procedure. Similarly, the crystallization and stability should be manageable by keeping as close to the lab procedure as possible. A medium risk was assigned since mixing during the crystallization and time are key scale factors that could result in differences between the lab and glass plant procedures. If the same process was assessed for later stage development, all of the unit operations would receive a medium to high priority since the process knowledge is limited.

The subsequent sections will discuss in more detail areas that should be considered when evaluating the development needs for a program. It is important to keep in mind that these factors are not independent and therefore a compilation of factors may in itself be a driver for development.

TABLE 20.4 Step Assessment for Example 20.1

Unit Operation	Risk to			Priority
	Safety	Quality	Business	
Activation	Unknown—no apparent exotherm	Unknown—no observed degradation	Incomplete activation leading to low yield	Low
Reaction and quench	Highly exothermic, HCl liberated	Key impurities form at higher temperature	None	High—impurity formation and exotherm must be understood and controlled
Crystallization	Highly acidic	Key impurity rejection	None	Medium—key impurity rejection is sufficient but should be understood
Isolation	None	Impurity A is removed during the cake wash	None	High—process impurity A must be controlled
Drying	None	None	None	Low
Impact of time	None	Unknown		Medium—effect of age time should be understood

20.2.1 Process Safety

In general, safety is a risk to be understood and then managed. For most risks, mitigation strategies can be developed, once the risk is understood and acceptable risks have been defined. The definition of acceptable risk will likely change as the scale of operation increases and this could drive process development as the project moves forward along its timelines. For example, the safety analysis for a $\leq$20 L scale-up may be limited to a paper review when no sign of exotherm has been observed, whereas at larger scale thermal and corrosion testing would be required.

20.2.1.1 Personnel Safety The safety issues related to personnel may include exposure to highly potent and toxic compounds (i.e., teratogens, mutagens), sensitizers, and genotoxic and cytotoxic intermediates. Highly potent and toxic compounds are usually characterized by having an exposure limit $<1\,\mu g/m^3$. The majority of pharmaceutical intermediates have exposure limits in the 10–100 $\mu g/m^3$ range. Compounds with exposure limits of 1–10 $\mu g/m^3$ are considered to have medium to high potency/toxicity [12]. Personnel risk can typically be managed by a combination of engineering controls such as closed isolation and handling equipment, personnel protective equipment (e.g., breathing apparatus and chemically resistant clothing, gloves, and face/eye protection), and administrative controls such as restricted access and specialized training. With advances in containment technology, exposure levels down to $<1.0\,\mu g/m^3$ can be achieved. This level is typical of exposure guidelines for compounds considered to be highly potent and toxic. However, the cost associated with purchasing and maintaining the appropriate high containment equipment for highly potent and toxic compounds can drive the decision to look for an alternative chemistry route when possible.

20.2.1.2 Exceptional Process Hazards The assessment of a process should include investigating exceptional process hazards. In general, pilot-scale and manufacturing facilities are set up to handle a "typical process," so variables such as high or low temperature (−20 to 110°C), solids charging, and slight exotherms ($\Delta T_{ad} < 5$°C) would not be considered unusual when performing a hazards assessment. However, many processes have one or more steps that include additional hazards such as gas evolution, dust explosion, and static and/or significant exotherms (Table 20.5). Such hazards need to be addressed with further development or by appropriate equipment selection, additional engineering controls, and personnel training.

In the case of gas evolution, understanding the chemistry and particularly the source and identity of the gas is important. Generation of CO_2 as a by-product in a reaction may not pose a significant risk, if the total gas generated is too low to result in a significant pressure increase for the processing equipment or if the rate of CO_2 evolution can be controlled by adjusting reaction rates or reagent addition times. However, if the amount, gas composition, or generation rate are not understood, further development is necessary to ensure that the gas evolution does not pose a significant hazard. Release of a flammable gas such as hydrogen poses an additional challenge since it has a wide flammability range (4–75% in air) and low minimum ignition energy [16].

20.2.1.3 Material Compatibility Material compatibility refers to the ability of the materials in a given equipment train to withstand exposure to the process streams (i.e., to maintain mechanical integrity at the temperature and timescale for the process). Most lab development occurs in glassware using Teflon accessories (agitators, seals, etc.), which ensures compatibility with the exception of hydrogen fluoride. In the pilot plant and manufacturing facilities, the range of

TABLE 20.5 Exceptional Process Hazards

Hazard	Safety Limit	Risk	Mitigation Strategy
Gas evolution	Dependent on equipment vent capacity and gas properties (i.e., minimum ignition energy, flammability)	Equipment overpressure, hazardous or combustible gas release	Understand gas formation mechanism to develop control strategy
High exotherm [13]	$\Delta T_{ad} > 50°C$, $TMR_{ad} \leq 24$ h. *Note:* Proximity of th operating temperature to the initiation temperature for secondary decomposition exotherms should also be considered	Runaway reaction and potential thermal explosion	Control reaction by addition method and cooling, maintain reaction sufficiently, maintain distance from decomposition exotherm. Training and awareness
Dust explosivity [14]	KST $\geq$ 1 bar m/s	Potential explosion	Based on explosion risk, consider not isolating, alternative form, or alternative intermediate. Inert handling, containment, explosion suppression, blow out panel. Training and awareness
Static [15]	$<$100 pS/m nonconductive	Arching from static charge buildup leading to risk to personnel, equipment damage (glass or Teflon), fire, and/or explosion	Bonding and grounding, inert handling, antistatic additives, solvent changes, conductive components (pumps, antistatic bags), appropriate hold times to match relaxation time for solvent. Training and awareness
Hydrogenation [16]	Concentration $<$4% or $>$75%	Potential fire and/or explosion, hydrogen embrittlement	Pressure testing, inert handling, grounding, explosion protection systems, hydrogen/LEL monitoring, equipment selection (motor and equipment rating), H_2 rated flash arrestors, open to air venting handling procedures
Flammable liquids [16]	Flash point $<$60.5°C (closed cup)	Potential fire and/or explosion	Inert handling, bonding, and grounding

physical equipment (glass lined, stainless steel, hastelloy C, tantalum) will likely provide the flexibility to ensure a compatible fit for any process. However, an initial assessment is usually necessary to ensure that the equipment is properly selected. This understanding of materials and process stream compatibility is required to ensure that the right set of equipment is selected for any scale-up. It is also important to be aware of not just the raw materials (solvents, reagents), the intermediates, and the products, but also by-products in the process. Table 20.6 describes some common equipment materials of construction and materials to avoid. Though some plastics and elastomers are compatible with many solvents, leaching must be considered since it would be difficult to find an impurity leached from the polymer in the final API. In certain cases, compatibility issues may conflict. For example, the use of heptane in a highly acidic environment may present a glass (static) and hastelloy (corrosion) concern. Also, material concerns should be extended to include interactions of the process stream with jacket and condenser fluids. This is of particular concern with water-sensitive process steams.

Material compatibility will likely not play a significant role in driving process development for early and mid-stage processes unless the equipment available is limited. Even then, a development effort based on incompatibility is not necessary until the program progresses to full development. When transferring a process to manufacturing, it becomes highly desirable to reduce or eliminate materials' compatibility issues to allow easy movement of a process between facilities.

20.2.1.4 Hazardous Reagent Handling Highly hazardous reagents are materials that warrant special consideration as the general safety hazards are well known throughout the chemical industry. In general, these materials should be limited when developing a commercial process since the complexity associated with risk mitigation can be costly and difficult to manage. However, most highly hazardous materials have been well-studied and methods to mitigate the risk have been developed. Despite the added cost, it is not uncommon to use a hazardous material in early development when the scale-up is still limited and the risks are well-known

TABLE 20.6 Examples of Incompatible Materials

Equipment Material of Construction	Incompatible Material
Carbone (condensers)	Bromine, NMP
Glass	Hydrogen fluoride, inorganic base at high temperature
Stainless steel	Acids, acid salts, chlorinating reagents
Polypropylene (filter media)	Some solvents (i.e., methylene chloride, heptane, toluene)
Hastelloy B	Ferric and cupric salts
Elastomers (seals) [17]	Some solvents
EPDM	Organic chlorides, cyclohexane
Neoprene	Ethers, acetates, acids
Viton	Acetone, amines, ammonia, acetates, ethers, ketones, caustics

and can be mitigated. The key is risk awareness and communication to ensure that all parties involved are aware of the hazards and the necessary controls used to address them. Table 20.7 lists some examples of hazardous reagents used in API syntheses.

20.2.2 API Quality

Prior to use in human clinical studies, impurities and other foreign contaminants within the API must be controlled at a level specified according to regulatory guidelines. Quality in pharmaceuticals refers to adhering to these regulatory rules as well as understanding the impact of process variations. Similar to safety, product quality is a key development driver. In this section, we focus on discussion of key aspects of API quality: (1) critical quality attributes, (2) genotoxic risk, and (3) process robustness.

20.2.2.1 Critical Quality Attributes Critical quality attributes (CQAs) are quantifiable properties of an intermediate or final product that are considered critical for establishing the intended purity, efficacy, and safety of the product. For API, CQAs must meet specifications prior to release for formulation and eventual use in clinical trials or commercial production. These may include overall purity, levels of impurities, form, color, metals, solvent content, and powder properties (Tables 20.8–20.12). The selection of CQAs will be based on ensuring that the API does not pose a significant risk to patients.

For impurities, the target levels are conservatively set assuming a high dose of 1 g without consideration of the actual clinical trial dosage or therapy duration. It is therefore possible that if the risk is sufficiently understood and can be managed, these target properties can be adjusted to less conservative values for compound used at low dosage and/or in a short duration clinical study. The inability to meet a purity CQA will drive additional development. At early stages of development, this may mean developing a rework strategy for the API, and subsequently in later development, may entail obtaining a detailed and complete understanding of the mechanism of formation for a key impurity.

The powder properties of the API, such as particle size and morphology, can impact the design of the formulation as well as the formulation process performance, and need to be addressed in concert with drug product development. Particle size becomes more of an issue depending on the Biopharmaceutics Classification System (BCS) since the higher the solubility and permeability the less likely that a change in the particle size will have an impact (Table 20.13). The crystal form of the API will impact the compound's chemical and physical stability as well as its pharmaceutical properties (solubility, permeability). Most APIs are crystalline and can exist as different polymorphs, solvates, or salts, or as co-crystals with other organic compounds. An optimal crystal form needs to be selected based on its stability and pharmaceutical properties. Identification of the various forms and selection of the most appropriate form are primary objectives in early development of the compound.

Changes to CQAs of the API that significantly impact the drug product could impact the program's clinical timeline, if additional clinical studies are needed to demonstrate equivalency of the drug products.

20.2.2.2 Genotoxic Impurity Risk Genotoxic compounds have the potential to impact cells in a mutagenic or carcinogenic manner. All intermediates and known impurities present in the API need to be analyzed to assess their genotoxicity. This is typically done first by computerized structural analysis against a database of known genotoxic structural moieties (*in silico*) and then followed up with tests on bacteria (Ames test) to verify positive results. Genotoxic impurities present a significant challenge for drug development since they must be controlled to levels much lower than the standard HPLC detectability limit. The limits for these impurities are set based on daily intake (Table 20.14). Therefore, at high drug load, the limit may be so low that the impurity cannot be detected with standard analytical methods.

As with API quality attributes, the primary risk mitigation for genotoxic compounds is sufficient removal or prevention of its formation. The added cost associated with development of a control strategy and appropriate analytical testing methods makes the presence of genotoxic compounds a formidable development challenge [27]. The need to develop a control strategy for genotoxic impurities will often force a reexamination of the synthetic route to either eliminate the formation of the compound from the synthesis or move its formation earlier in the synthetic sequence, allowing the subsequent reaction, workup, and isolation steps to more effectively remove the impurity prior to the API step. If an intermediate is genotoxic, a new synthetic route that avoids the intermediate may be designed. In the case of an impurity,

TABLE 20.7 Examples of Hazardous Reagents

Chemical	Hazard	Risk Mitigation
t-Butyl lithium [16]	Pyrophoric, air sensitive	Proper handling and inert handling to prevent exposure to air
Azides (e.g., sodium azide) [16]	1. Under acidic conditions, sodium azide forms highly toxic and explosive hydrazoic acid gas 2. Sodium azide and hydrazoic acid are extremely toxic and can be absorbed through the skin 3. Heavy metal azides are shock sensitive	1. Proper use and waste handling techniques. Avoid contact with water or acid 2. When handling use impervious protective clothing and proper PPE (Personal Protective Equipment) 3. Plastic materials are preferred for handling or nonsparking metals
Hydroxybenzotriazole (HOBt, anhydrous) [18]	Explosive, flammable solid	Proper handling and storage. Avoid heat and mechanical shock. Consider use of the HOBt hydrate due to reduced explosivity risk
Alkali and alkaline hydrides (e.g., sodium hydride) [16]	Sodium hydride reacts violently with water. The heat given off is sufficient to ignite the hydrogen decomposition product. Sodium hydride is spontaneously flammable in air	Proper handling and storage. Avoid contact with water
Alkali metal cyanides (e.g., sodium cyanide) [16]	Highly toxic	Use only in well-ventilated area. *Note:* Hydrogen cyanide can be absorbed through the skin. Avoid contact with water or acid. Communicate the hazards prior to use
Hydrazine [16]	Highly toxic, highly explosive (limits in air 4.7–100%, flash point 52°C)	Proper PPE and communication of hazards prior to use. Maintain inert environment and avoid contact with oxidants and catalyst
Chlorinating agents (e.g., oxalyl chloride, $SOCl_2$, $POCl_3$, PCl_3) [19]	Highly toxic. React violently with water and release HCl gas. In addition, thionyl chloride ($SOCl_2$) and oxalyl chloride ($(COCl)_2$) release SO_2 and CO gas, respectively	Proper use and waste handling techniques. Avoid contact with water or acid. When CO and SO_2 gas release are anticipated, ensure proper ventilation and consider monitoring
Metal and supported metal catalyst (e.g., Pd or Pt on carbon, Raney nickel) [19]	Catalysts such as Raney nickel or activated heterogeneous catalyst such as supported Pt and Pd are pyrophoric. The risk of fire is especially high in the presence of flammable liquids	Proper use and waste handling techniques. Catalyst in contact with flammables should be kept under nitrogen inertion. When kept wet with water, Pt and Pd supported catalyst can be handled in air
Grignard reagents [20,21]	Grignard reagent formation and reactions are highly exothermic. The exotherm is particularly hazardous since the reaction initiation can be delayed. Grignard reagents react exothermically with air, water, and CO_2	Proper transportation, handling, and storage. Avoid contact with air and water. Evaluate the reaction exotherm and the equipment cooling capacity to ensure that proper control can be achieved. Charge no more than 20% of the reagent prior to reaction initiation. Consider online techniques such as FTIR to monitor the reaction progress. Evaluate the potential for water content including jacket services. Care should be taken when disposing of residual magnesium turnings
Halogenating agents (Cl_2, Br_2, I_2) [16]	Highly toxic vapors. Water reactive	Proper handling and storage to address inhalation hazards
Hydrogen flouride [19]	Highly toxic. Fluoride ion can penetrate skin and bind with ions such as calcium, potassium, and magnesium in the body	Select proper PPE to prevent inhalation or direct exposure. HF is incompatible with glass and most metals [16,17]
Phosgene [16]	Highly toxic gas. Reacts in lungs reducing lung function leading suffocation	1. Thorough plant controls to prevent emission 2. Leak detection devices and personnel monitors 3. Escape breathing mask or respirator

TABLE 20.8 Typical API Properties Analyzed Prior to Releasing the Material for Drug Product Formulation [22]

Property	Purpose
Purity/impurity profile	The weight percentage can be measured by HPLC or titration. An HPLC (High Performance Liquid Chromatography) purity profile can also show the impurity concentration and indicate whether there is a significant amount of unknown present. The purity of an API is regulated by ICH guidelines (Table 20.9)
Chiral purity	Chiral purity for single chiral center compounds is defined by the enantiomeric excess (ee) and is derived from HPLC using chiral columns. ee is defined as $(R - S)/(R + S)$, where R and S are the fractions of the enantiomers and $R + S = 1$. Chiral purity for diastereomers (multiple chiral centers) is also derived from HPLC
Crystal form (polymorph, solvate, salt)	Form is usually verified by X-ray powder diffraction (XRD), solid-state NMR (Nuclear Magnetic Resonance), or spectroscopic methods (i.e., Raman). The appropriate form ensures that the compound has good physical and chemical stability as well as pharmaceutical properties
Color	Color can be an indicator of an unidentified impurity or degradate. It is also important for ensuring a uniform tablet color. Color can be assessed visually or quantitatively with UV
Inorganic impurities (including metals)	Inorganic impurities can be quantified by residue on ignition or atomic adsorption spectroscopy. A generic heavy metals test is performed by ICPMS (Inductively Coupled Plasma Mass Spectrometry). In addition, individual metals known to be present in the process streams such as Pd and Pt are monitored and need to be controlled based on dose. A typical target for heavy metals is $\leq$10 ppm [23]
Solvent content (including water)	A GC (Gas Chromatography) analysis of the final API is performed specifically looking for any solvent present within the final two API synthesis steps. Solvents have differing level of toxicity and therefore different target limits (Tables 20.10-20.12). Residual water is important for compounds that are hygroscopic, degradable by moisture, or known hydrates. Standard methods include Karl Fisher titration or loss on drying
Powder properties	Typically, particle size measured by laser diffraction, crystal habit assessed by microscopy, and form measured by XRD or Raman are of primary concern. Other measures such as surface area and density may also be appropriate. Powder properties can have a significant impact on the formulation process and the API's bioavailability
Microbial limits	Such assays include total count of aerobic microorganism, yeast or molds, and absence of specific bacteria. The need for such testing is based on nature of drug substance and intended use of drug product (e.g., endotoxin testing for drug substance to be formulated into injectable drug product)

a detailed understanding of how the impurity forms may afford a method to limit or prevent the formation. Typical control strategies for the impurity might include reaction conditions and/or extraction and crystallization design.

20.2.2.3 Process Robustness The ability of a process to demonstrate acceptable quality and performance while tolerating variability in inputs and process parameters is referred to as robustness [28]. Robustness is a function of both the process design (synthesis route selected, the equipment capabilities and settings, and environmental conditions) and the process inputs (quality of raw materials). Process robustness and therefore process understanding is of critical importance to enabling commercialization of a drug. The use of in-process controls and assays ensures that processing activities produce API with the required quality. Understanding of the process variability is critical to ensuring that the API quality will be consistently achieved.

As a project moves into full development and toward commercialization, increased emphasis is placed on under-

TABLE 20.9 International Conference on Harmonization Reporting Guidelines for Impurities Present in an API [8]

Maximum Daily Dose[a)]	Reporting Threshold[b)]	Identification Threshold[c)]	Qualification Threshold[d)]
$\leq$2 g/day	0.05%	0.10% or 1.0 mg/day intake (whichever is lower)	0.15% or 1.0 mg/day intake (whichever is lower)
$>$2 g/day	0.03%	0.05%	0.05%

[a] The amount of drug substance administered per day.
[b] The reporting threshold is a limit above which an impurity should be reported. Higher reporting thresholds should be scientifically justified.
[c] Identification threshold is a limit above which an impurity should be structurally identified.
[d] Qualification threshold is a limit above which an impurity should be qualified in clinical studies. Lower thresholds can be appropriate if the impurity is unusually toxic.

TABLE 20.10 ICH Class 1 Solvents Should be Avoided for Use in Drug Substance Synthesis [8]

Solvent	Concentration Limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

TABLE 20.12 ICH Class 3 Solvents May be Regarded as Less Toxic and of Lower Risk to Human Health [8]

Solvent	PDE (mg/day), Concentration Limit (ppm)
Acetic acid Acetone Ethanol Ethyl acetate Heptane Isopropyl acetate Methyl ethyl ketone Methyl isobutyl ketone Isopropanol	Class 3 solvents may be regarded as less toxic to human health and need to be controlled to <0.5% or 50 mg/day. This specification does not require specific testing as long as the product loss on drying test is less than 0.5 wt%

standing which step and process parameters have the potential to impact an API CQA. A design range for these parameters can then be defined to ensure that the API quality is consistently achieved. Within the design range, a target set point is selected and the process and equipment capability are then used to define a normal operating range. Critical process parameters (CPPs) are parameters that have a direct and significant influence on a CQA when varied beyond a limited range. Failure to operate within the defined range leads to a high likelihood of failing a CQA specification. Numerous approaches have been presented on defining this range to distinguish a CPP from non-critical process parameters. One approach is to evaluate whether material of acceptable quality can be made within 6σ of the normal operating range, where σ is the equipment specific operational variability [29].

Building process knowledge is typically a significant undertaking in the later stages of development since each unit operation may have up to 10 process parameters, and it is unlikely that each of these process variables has been studied. For example, for a given reaction, process parameters could include reaction temperatures, time to ramp up to the temperature, reaction time at temperature, agitation, variability of charge equivalents, sequence of charges, hold times between charges, and concentrations. An earlier stage assessment would likely focus the development effort only on a subset of these parameters with the largest impact on process robustness. In addition, the potential for multivariable interaction such as time and temperature must be evaluated at later stages.

An important component of process robustness for a given step is the understanding of process impurity generation and rejection. It is then necessary to determine the "fate" of the impurity in later processing steps; more specifically, is it inert or transformed into other process impurities and is the original impurity or new impurity removed during an extraction or crystallization. By carrying this analysis forward through the API step, the impurity "tolerance" or limit can be established. Target purity profiles for each intermediate can then be defined through similar analysis with all process impurities. This assessment is often completed to support the establishment of the appropriate critical quality attributes for the drug substance.

20.2.3 Business Optimization

In the absence of quality or safety issues, process development is driven by optimization of parameters to improve the business of manufacturing drug substance (e.g., productivity, flexibility, or throughput). Often, the majority of this development effort can be deferred until there is a high probability that the compound will be commercialized. A key milestone for any compound is the achievement of proof of concept in

TABLE 20.11 ICH Class 2 Solvents Should be Limited Because of Their Inherent Toxicity [8]

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
N,*N*-Dimethylacetamide	10.9	1090
N,*N*-Dimethylformamide	8.8	880
Methanol	30	3000
N-Methylpyrrolidone	5.3	530
Tetrahydrofuran	7.2	720
Toluene	8.9	890

TABLE 20.13 Biopharmaceutical Classification System [24]

Class I	High permeability,[a)] high solubility[b)]
Class II	High permeability, low solubility
Class III	Low permeability, high solubility
Class IV	Low permeability, low solubility

[a] A drug substance is considered *highly permeable* when the extent of absorption in humans is determined to be >90% of an administered dose, based on mass balance or in comparison to an intravenous reference dose.
[b] A drug substance is considered *highly soluble* when the highest dose strength is soluble in <250 mL water over a pH range of 1–7.5.

TABLE 20.14 FDA Draft Guidance on Genotoxic Impurities [25, 26]

Duration of clinical trial exposure	<14 days	14 days to 1 month	1–3 months	3–6 months	6–12 months	>12 months
Allowable daily intake	120 μg	60 μg	20 μg	10 μg	5 μg	1.5 μg

the therapeutic hypothesis, typically successful completion of phase IIA clinical trials. However, the complexity of the process and the duration of the overall clinical program will play a role in assessing the timing of process optimization.

There are two key business drivers for API process development: (1) meeting the project timeline and (2) reducing the cost of manufacturing. The first driver applies to both early- and late-stage products. The second priority, reducing the cost to manufacture, is not usually considered in the early stage of development unless there are specific issues that will impact scale-up to generate the required quantity of API for the program's development. Reducing the cost of manufacturing involves both synthesis design to reduce the material cost and number of steps as well as process optimization to address productivity and capacity through improvements in yield and volume efficiency.

As part of the business drivers for process development, we examine the impact of project timelines, process fit and ease of manufacturing, and process greenness. Evaluation of a process' productivity and fit into a manufacturing plant through time cycles, yield, and mass balance will also provide insight into setting the direction for process development. The use of process metrics is an important tool that will enable a common platform to evaluate the evolution of a process.

20.2.3.1 Project Timeline Hierarchically, the project timeline does not drive development but rather the development strategy. Generally, this timeline will define both immediate and long-term API needs. The immediate needs are driven by API required for the clinical studies, the drug safety studies, and drug product development. All of these activities are on the critical path to bringing a drug to market. The highest business priority is delivering sufficient API to meet the clinical and drug safety study timelines. The short-term needs may drive changes, which will be covered in the next few sections. In the long term, the project timeline will drive development decisions. With an extended project timeline due to long clinical trials (10–14 years), deferring process development focused on optimization allows resources to be used on programs with shorter timelines. Alternatively, an accelerated program (5–7 years) leaves little time for process development and may drive parallel development efforts to meet short-term needs as well as to develop the manufacturing process.

20.2.3.2 Process Cycle Time At commercial scale, an optimized cycle time is critical to control cost and manufacturing capacity utilization. The process cycle time can be thought of at multiple levels including the time to complete (1) the entire synthetic sequence, (2) one isolated intermediate or process step, and (3) an individual unit operation. In early development, optimization of the cycle time is less critical. Time cycle optimization would only be considered in the rare case when the program timeline cannot be met. Even then, the first choice would be to use alternative equipment such as a larger vessels or filters to accelerate the timeline. At the transition to full development, a significant effort will be placed on improving the overall process cycle time. This timing will vary depending on the severity of the bottleneck and the potential for changes to impact the API quality. As a project moves through development, emphasis will shift from individual step and unit operation optimization to debottlenecking of the whole synthetic sequence. In development, individual batches are typically run in sequence, so a reduction in time anywhere will lead to a shorter overall delivery time. At commercial scale, the process unit operations and process steps will likely be run in parallel, so resources should be more strategically placed on true bottlenecks. These bottlenecks will not likely be known until the commercial process fit is identified since multiple unit operations may be planned for the same equipment. This is most often the case with isolation and drying where filtering on a centrifuge and drying in a conical dryer can process in parallel whereas filtration and drying on a filter dryer must occur in series.

As an example, a simple process timeline involving a reaction, aqueous workup, solvent swap, crystallization, isolation, and drying steps is depicted in Figure 20.1. For ease of discussion, each of these steps is assumed to have an 8 h cycle time. The first timeline illustrated is a process fit with two vessels and a filter dryer. During the isolation step, both the crystallizer and the filter dryer are active, which extends the time cycle in the crystallizer. In the second timeline, the fit is the same, but the equipment downtime has been minimized by running processing steps in parallel. This provides a significant improvement in time cycle allowing the third batch to be completed in a similar time frame as the second development batch. The bottleneck, however, in this process is vessel 2, as it requires 24 h versus the 16 h for all other equipments. If you add an additional vessel to hold the slurry during isolation, as shown in the third timeline, the parallel processing timeline is reduced by 8 h. An alternative approach to debottleneck is a focused development effort on reducing the total time cycle to complete the solvent swap, crystallization, and isolation. It is therefore important to

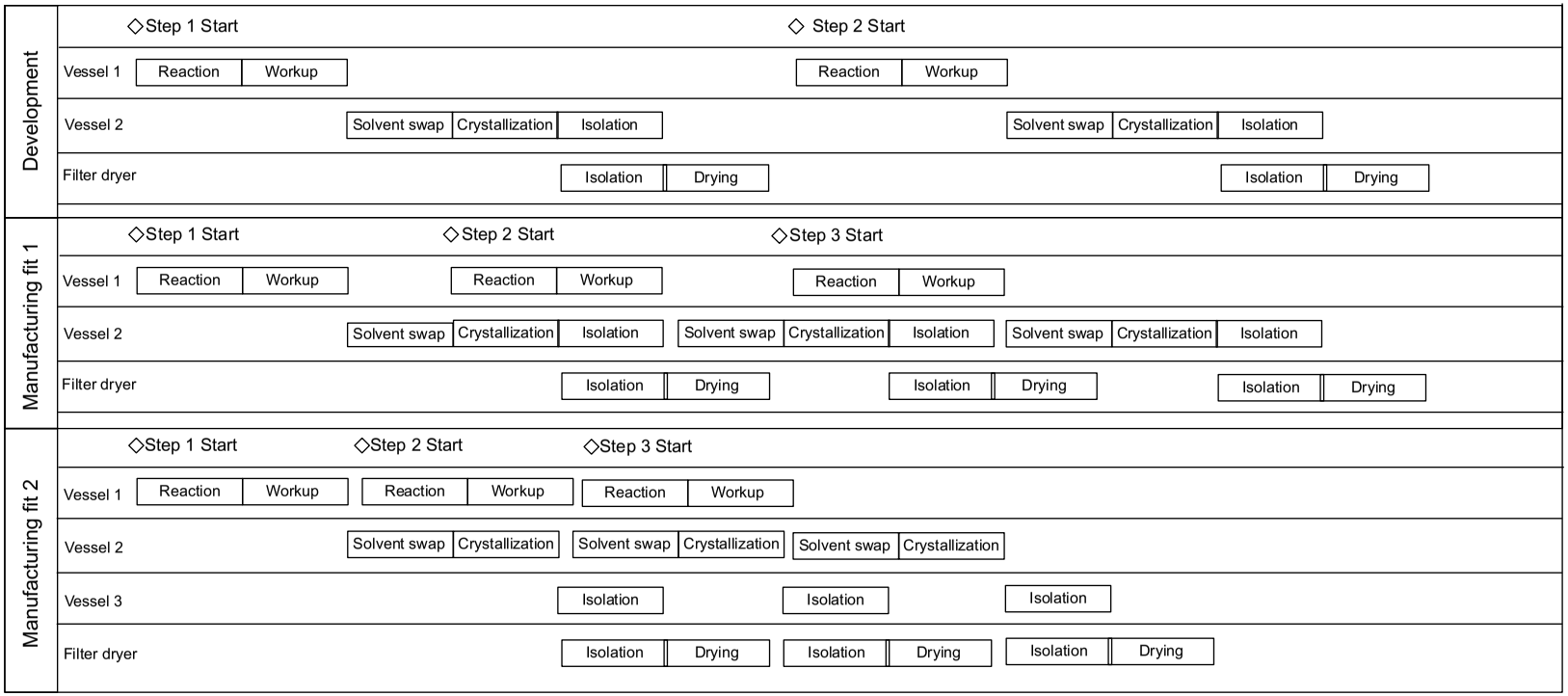


FIGURE 20.1 Single-step processing timeline.

evaluate the process as a whole. In this case, the only equipment change that would optimize the process time cycle is debottlenecking vessel 2. Similarly, the process as a whole should be considered when evaluating where to focus the development effort. In this example, all steps were assumed to take the same amount of time, whereas in reality the processing time for each unit operation will vary widely and should be considered in the evaluation.

20.2.3.3 Process Fit and Ease of Manufacture The process design can have a significant impact on the manufacturing cost and flexibility as well as the process portability. Ideally, a process is flexible enough to fit into any facility, regardless of the equipment available. However, there are often process constraints such as volume requirements as well as specialized processing equipment needs such as hydrogenators, cryogenic reactors, or continuous processing that impact the selection of manufacturing equipment. In early development, process fit is of little concern since the equipment flexibility is built into glass plant and pilot-scale facilities. However, as a project moves toward full development, the flexibility of the process becomes a significant development driver. In general, development would focus on improving the process flexibility and reducing the process complexity. Therefore, as a project moves toward full development, the desire to reduce the equipment cost and operational complexity may mean minimizing the use of specialized technology.

The first step in improving process fit and ease of manufacture is minimizing the number of unit operations by reducing the need for solvent exchanges, extractions, and isolations. In early development, the process may not be well understood and process steps are added to ensure that a quality material is achieved. An increase in process knowledge around impurity formation and control will allow optimized solvent usage and may allow for the elimination of extractions and isolations. Once the process steps are defined, a high priority is placed on reducing the maximum process volume as well as providing a wider volume range. For a given process train, the maximum volume will dictate the maximum batch size and therefore manufacturing efficiency. Outside of volume reduction, the goal is to crystallize product that can be isolated and dried in either a filter dryer or a centrifuge and conical dryer. Flexibility in crystallization, isolation, and drying are typically linked. Regarding reactions, flexibility in scale-up is typically associated with mixing in heterogeneous systems. It is often not possible to eliminate heterogeneous reactions, so the focus is placed more on understanding and minimizing the impact at scale. Similarly, while hydrogenations can impact the process fit, it is often a very efficient chemical transformation and in the case of asymmetric hydrogenation can significantly increase the overall process yield.

20.2.3.4 Process Greenness Process greenness is typically considered as part of the overall development strategy to select the final synthetic route and is rarely the main driver for process development. This is especially true in early development where the waste treatment cost and environmental impact are minimal. There are many aspects to consider when discussing process greenness. The most general methods such as the *E*-factor or the process mass intensity (PMI) account for the total waste or mass used relative to the product mass. These factors align quite well with business priorities since it would drive development toward lower cost by reducing material requirements, volatile organic carbon emissions, and chemical wastes. Though these factors give a quick guide to compare the efficiency of materials used, they fail to account for safety and environmental risks posed by specific reagents and solvents. Therefore, the *E*-factor and PMI are typically used only as an early guide. As a program moves through to full development, a more comprehensive evaluation is performed and includes reagents' and solvents' risks. An example of such a tool is the process greenness scorecard, developed by Bristol–Myers Squibb, which tracks about 15 parameters for each step in process and uses green chemistry and engineering principles to assign values that are weighted into an overall score [30]. It is important to note that the definition of process greenness is continually evolving toward a more holistic evaluation. Some proposals include factors such as the impact of operating temperature and certain inefficient unit operations such as classical chromatography [31,32].

20.2.3.5 Yield and Mass Balance The yield and mass balance are key indicators for the process and, with the exception of early development, drive the team toward further development. The two key measures of yield and mass balance are the absolute number and the batch-to-batch variation. The target yield and mass balance will vary based on the step complexity; however, a target yield of 80–90% and mass balance of $>95\%$ are typically acceptable. Though a low yield and/or mass balance are of concern as a process moves through development, a focused development effort to improve yield and mass balance is likely not justified if the process is consistent. However, significant batch-to-batch variability in both yield and mass balance is an indication that a key parameter in the process is not well understood. This lack of knowledge is a critical issue that should be considered even in early development since the quantity or quality of the API synthesized in a given scale-up campaign is at risk. Therefore, even in early development, an effort should be made to understand significant inconsistencies in yield or mass balance.

20.2.3.6 Process Metrics In the previous sections of this chapter, numerous factors to assess a given process have been discussed. Process metrics can be a powerful tool to evaluate

TABLE 20.15 Process Metrics for a Process Step

Productivity metrics	Yield (mol%)
	kg intermediate/kg API
	Number of chemical transformations
	Longest reaction time (h)
	Number of workups (count of below total)
	• Distillations
	• Extractions
	• Waste filtrations
	• Chromatography
	Peak V_{max} (L/kg)
	V_{max}/V_{min} (V_{max} swings)
Material usage and waste generation	kg starting material/kg product
	kg reagents/kg product
	kg aqueous charges/kg product
	kg solvents/kg product
Quality metrics	Purity (wt%), normalize for salts, solvates
	Purity (% A)
	Potential GTIs
	Impurities above ICH identification threshold
	Number of unknown impurities

the quality and business drivers for process development as well as to track the process evolution. Table 20.15 lists example of process metrics to consider for a given process step. Such process metrics can then be tabulated for a given synthesis step or summarized for the entire synthetic sequence (Table 20.16).

20.3 UNIT OPERATIONS

In assessing the suitability of a process to run at a given scale, there needs to be an assessment of both the overall characteristics of the process such as cycle time, cost of goods, and yield (as described in Section 20.2) and the characteristics of each individual unit operation. This section will examine the most common unit operations and enumerate factors that contribute to the scalability of each operation. These factors should be considered in a process scale-up assessment.

TABLE 20.16 Process Metrics for an Overall Synthesis

Overall Yield
Total kg intermediates/1 kg API
Total number of workup operations
Total number of isolated intermediates
Total number of potential GTIs
Total kg solvents/kg API
Total kg aqueous/kg API

20.3.1 Introduction to Evaluation

One of the hallmarks of a readily scalable process is that it can be run in a standard facility, using standard equipment, with an ordinary degree of control over the process parameters. Therefore, it is critically important for an engineer to understand how processes are generally run on pilot and manufacturing scale.

The vast majority of pharmaceutical processes are run as a batch operation, rather than as a continuous or semicontinuous operation. The process train typically consists of multiple stirred vessels, pumps and lines for liquid charges/transfers, waste receiver vessels for distillate, mother liquors, and waste streams, product isolation equipment (pressure filters, centrifuges, or filter dryers), and dryers (tray, conical, rotary, filter dryers). The batch reactors are generally equipped with ports for charges/feeds/probes, a bottom valve for discharge, a fixed agitator type and fixed baffling configuration, and overhead piping system for providing venting, vacuum, and emergency pressure relief, typically with a condenser on the main vent path. Flexible lines and a manifold system are commonly used to allow transfers from vessel to vessel, or from vessels to the isolation equipment. Common instrumentation on the equipment includes the temperature and pressure of the equipment's contents, the temperature of the equipment's jacket, and product stream's density.

Given the standardized nature of the equipment, standard unit operations are preferred to achieve the process goals. A typical sequence of unit operations includes solution preparation, reaction, separation (extraction, distillation), crystallization, isolation, and drying.

20.3.1.1 Selection of Unit Operations Before the sequence of unit operations for a given step can be determined, an understanding of the objectives for the step is needed. The objectives of each step in the synthetic sequence should be considered collectively, since there are likely trade-offs between steps in the sequence with respect to yield, quality, process cycle time, and the need for specialized equipment. Key to assessing these trade-offs are well-established API quality requirements (including powder property requirements), and knowledge of the material value for a given step (e.g., what is the value of an additional 5% yield). The intermediate quality requirements can then be defined after considering trade-offs between the steps. For example, one may tighten the quality specification in an early step at the expense of step yield, in exchange for eliminating the need for difficult or costly purification downstream.

Once the objectives for the overall step are established, the objectives of each individual unit operation should be understood. An optimized process will involve no additional operations (or more complicated operations) than needed to safely, reliably, and robustly meet the process objectives.

Prior practice at smaller scales may dictate the initial choice of unit operations, but as the process is optimized the number and type of operations are expected to change. For example, a prior iteration of a process may involve multiple liquid–liquid extractions, designed to remove a key process impurity. If subsequent improvement to the reaction conditions reduces the number or extent of side reactions, fewer or no extractions may be needed. The process optimization to reduce the number and complexity of unit operations is a key process development objective.

20.3.1.2 Process Fit Another core process engineering activity is understanding the process fit. Engineers are frequently tasked with fitting a process in an existing facility in such a way to minimize capital expenditure (modifications to existing equipment or purchase of new equipment) and to minimize the deployment of shared resources (portable equipment). To accomplish this task, the engineer must clearly understand the capabilities and limitations of the plant. Specifically, vessel configurations (minimum and maximum volumes, baffles, number and type of agitators), vacuum and temperature control capabilities, heat and mass transfer coefficients, filtration capabilities (e.g., centrifuge versus pressure filter, filter area, filter porosity), and drying capabilities (e.g., agitated versus nonagitated, heat transfer, vacuum control) will need to be considered. The engineer will then be able to assess if the process as designed can operate in the plant without modification and, if necessary, modify the process to fit existing equipment.

20.3.1.3 Common Scale-Up Factors There are many scale-up factors that are not specific to any one particular unit operation. Time is a particularly important example. Nearly every activity requires more time to accomplish at manufacturing scale compared to the lab scale. The ramifications of this will be discussed in the individual unit operations section. One concern that is common to all the unit operations is stability. The stability of the reaction mixture with respect to undesired side reactions (degradation) must be assessed for each unit operation on timescales relevant to the plant scale.

Another issue common to most unit operations is the potential for residual material in process lines and dead legs to interact with material being charged or discharged. For example, a single charge line may be reused for multiple reagent charges, with a solvent flush in between each charge. If the flush is inadequate (or not done), and the materials are not compatible with each other, a deleterious reaction may occur. It is critically important for both safety and quality reasons for the engineer to be cognizant of what lines are being used for what purpose, and to systematically consider what residues may be left behind as process fluids are transferred throughout the equipment train.

For all unit operations where heat transfer is important, the surface area to volume ratio will be a common issue. As scale (vessel size) increases, the surface area to volume ratio decreases. Since the rate of heat flow is proportional to the heat transfer area, and the overall heat capacity of the system is proportional to the mass of the batch (and thus the volume), heat transfer will be significantly slower as a process is scaled up.

For the reaction, extraction, and crystallization unit operations, mixing is a common scale-up factor. Generally speaking, the mixing power is much greater in the plant than in the laboratory. It can be challenging to simulate the mixing behavior that will be obtained on scale in the laboratory, since there are many variables one can choose to hold constant between the experiment and the plant run. These variables include power, power per volume, tip speed, rotational speed, flow per volume, torque per volume, Reynolds number, blend time, and geometric similarity (ratio of impeller diameter to vessel diameter). Different phenomena scale with different variables, and it is not always well understood which variable is the best choice for scale-up and scale-down. Some case studies and rules of thumb are available in the literature [33, 34].

A final consideration that applies to several unit operations is the issue of dip tube depth. For any operation that involves sampling, the engineer must consider whether or not the dip tube is below the liquid level, to allow a sample to be taken. In this case, the minimum volume for a unit operation may need to be increased.

The following sections discuss the common individual unit operations. Detailed treatment of the chemical engineering theories of heat transfer, mass transfer, thermodynamics, chemical kinetics, etc. and their application to batch reactors is available elsewhere, and is outside the scope of this chapter. Instead, a brief discussion of the factors an engineer needs to consider is presented.

20.3.2 Reaction

The objective of the reaction unit operation is to convert a starting material or materials into the desired product, with maximum yield and minimum degree of by-product (impurity) formation. In the laboratory, reagent selection, solvent selection, stoichiometry, sequence of addition, and temperature are generally established. This list of process variables is unlikely to change upon scale-up, since, as Caygill et al. [35] state, “chemical rate constants are scale independent, whereas physical parameters are not.” The many physical parameters that play a role in the outcome of the reaction that are scale dependent (see Table 20.17) are the main cause of scale-up problems.

A key consideration is whether the reaction is homogeneous (single phase) or heterogeneous (multiphase). Generally speaking, a standard batch reactor is configured such that

TABLE 20.17 Scale-Up Factors for Reactions

Factor	In Lab	At Scale	Impact	Means to Evaluate
Time to charge reagents	1 min or less	Between 5 and 60 min	Different stoichiometry profiles with time may impact reaction kinetics	Simulate longer additions at lab scale
Charge method	Pouring, pump, addition funnel	Pump from drum, pressure from vessel, vacuum from drum	Choice of charge method may impact rate. Vacuum charges may cause volatilization of components	Simulate charge method
Charge port	Generally above surface	Above-surface, subsurface, sprayball	Backmixing may occur during subsurface charges. Use of above-surface ports may leave material on the vessel walls. Use of sprayball can help rinse solids from sides of the vessel	Backmixing calculation from engineering correlations [36]
Sequence of addition	Based purely on chemistry/convenience	Limited number of lines and ports may necessitate different order of addition (e.g., to avoid incompatibles in the same line). Also, order of solids versus liquids may differ in the plant based on considerations such as inert handling	Can affect the kinetics of main and side reactions	Test different orders of addition in lab experiments
Mixing time	Can vary over wide range	Varies, max agitation likely affords longer mixing time than lab maximum	If reaction time is fast compared to mixing time, undesired reactions may occur	Experiments to determine reaction kinetics + blend time calculation. Can evaluate Damköhler number. If large, mixing is an issue
Solids suspension	Typically not an issue	May be an issue	Insufficient suspension equals lower effective surface area of solids	Njs (agitator speed to just suspend) calculation [37]
Mass transfer	$k_{La} = 0.02–2\ s^{-1}$	$k_{La} = 0.02–0.2\ s^{-1}$ (batch reactor), $k_{La} = 1–3\ s^{-1}$ (Buss Loop)	Either mass transfer or chemical kinetics may be rate limiting at different k_{La}. This will impact reaction profile	Gas uptake experiments in lab and at scale to determine k_{La}. k_{La} predictions by engineering correlations
Heat transfer	Excellent, high area/volume	Lower area/volume as scale increases	Safety (runaway reaction), excursion from acceptable temperature range	UA evaluation at scale (mock batch/solvent trial heating trend data may be used) and in the lab

reagents in a homogeneous reaction can be sufficiently well mixed to avoid the need for detailed consideration of mixing and mass transfer. There are, of course, exceptions, such as highly exothermic reactions, where temporary hot spots can cause a high level of impurity formation before reagents are well-mixed. In contrast to homogeneous reactions, heterogeneous reactions (reactions with separate liquid–liquid, liquid–solid, or liquid–gas phases that participate in the reaction) are likely to be highly dependent on mass transfer considerations.

Table 20.17 enumerates several scale-up factors for reactions.

TABLE 20.18 Scale-Up Factors for Extractions

Factor	In Lab	At Scale	Impact	Means to Evaluate
Tendency to form emulsions	May be seen	Additional factors cause emulsions to be seen even if not seen in lab (e.g., increased agitation power)	Stable emulsions must be broken before processing can continue	Test extremes of composition. Maximize mixing to stress. See text for means to break emulsions
Settling time (settling velocity)	Variable	Variable	Settling *velocity* should be similar between lab and plant. Settling time therefore will be much longer in a plant vessel	Measure settling time and height of phase boundary in the lab. Estimate time on plant scale using constant velocity
Mixing	Shaking in sep funnel, stir bar, overhead stirring. Generally easy to mix the phases, but low power	Various agitator, vessel, and baffle configurations. Much greater power. For fixed equipment operated within normal volume ranges, mixing is typically good	Adequate mixing needed to properly mix the phases and equilibrate composition. Excessive agitation may promote stable emulsion formation	Determine at-scale blend time to ensure that phases will be adequately mixed. Stress the process by mixing as vigorously as possible in the lab
Ability to catch the split	Generally easy	May be difficult to see through small sight glass. Use of mass meters to detect density differences to determine split	Missing the phase boundary can cause repeated operations (waste of time) or loss of yield	Note when the phase boundary is more difficult to see (e.g., phases have similar phase color and opacity) and inform the plant staff of the need for caution. Before plant run, calculate expected phase volumes, so that the rate of discharge can be adjusted depending on how close the phase boundary is
Rag layer	Minimal or not seen	Rag layer of significant volume may be present	Must determine disposition of rag layer in advance—inclusion can affect purity, exclusion can affect yield	Difficult to assess in lab. Establish rag layer disposition in advance of processing based on quality/yield requirements. Typically, rag layer is kept with the product phase, except for the final phase split

20.3.3 Separation

20.3.3.1 Extraction The objective of an extraction unit operation is to remove undesired components (organic impurities, inorganic salts) from the product solution, and in some cases to quench the reaction. This is achieved by adding a liquid that is immiscible with the reaction mixture. Typically, the reaction mixture is organic and the added liquid is water or an aqueous salt solution, but the reverse situation is possible. In the laboratory, the liquid is added to the vessel and stirred, or the liquids are combined in a separatory funnel and shaken together. The agitation is stopped and the phases are allowed to settle, followed by separation. The relative densities of the phases are a key parameter in determining how quickly the phases will settle. Table 20.18 enumerates several scale-up factors for extraction:

Emulsions Several differences between the lab and the plant scale can contribute to emulsion formation. One is the mixing power per volume. Most often the plant-scale agitation is high power per volume, and thus there may be a greater tendency to form emulsions. Another factor is the likelihood to precipitate either product or salts during the extraction. In the laboratory, the midpoints of acceptable temperature and solvent composition (distillation end points, charge ranges) are often studied, whereas in the plant the parameters may be near the upper or lower part of the range. If one of the phases is near the solubility limit for a component, tiny particles that have the potential to stabilize an emulsion may form. Also, at scale the reagents may introduce tiny particulates or impurities that affect solubility. A final consideration is the position of the agitator blade relative to the phase boundary. This can influence which phase is dispersed in which, potentially affecting the stability of the dispersed phase. These factors may be proactively investigated in the laboratory to determine if an emulsion is likely.

If an emulsion is formed, methods to break the emulsion should be studied. If the emulsion is seen for the first time in the plant, such a study may be undertaken with a batch sample. Typical means of breaking an emulsion include addition of either solvent or water to change the composition, heating, filtration (to remove stabilizing entities such as tiny particles), pH adjustment, salt addition, and in rare cases, addition of a demulsifier. Some case studies and rules of thumb are available in the literature [38].

20.3.3.2 Distillation Generally, the objective of a distillation operation is to change the solvent composition of the system to facilitate downstream processing. This is generally performed in a semi-batch mode by either continually adding the new solvent at a constant volume or sequentially adding the new solvent and then distilling down to the original volume, sometimes repeatedly (put/take). More rarely, reactive distillation may be used in cases where a volatile component must be removed to drive the reaction to completion. Distillation is also occasionally used to change the solvent composition to drive crystallization of the product (distillative crystallization).

A good first step in understanding a distillation operation is to obtain thermodynamic vapor–liquid equilibrium (VLE) data for the solvent system in question. The effect of pressure, the presence or absence of azeotropes, and the difference in vapor compositions across the liquid composition space are all easily visualized (for two solvent systems) with a x–y or T–x–y diagram (or several diagrams for different pressures). Several software packages (e.g., DynoChem™, Aspen™) are available to perform VLE calculations and distillation simulations. Typically, calculations and simulations based on pure solvents (ignoring the presence of the product or starting material) provide sufficiently accurate estimates.

Table 20.19 enumerates several scale-up factors for distillations:

20.3.3.3 Color/Metal Removal The objective of a color or metal removal unit operation is to purify the process stream with respect to color bodies or metals. Typically, this is accomplished through the use of an adsorbent material. Common examples include activated carbon, functionalized silica, or functionalized polymeric materials. Use of this unit operation at scale is not desirable since color and metal removal requires special materials and often special equipment. If other means of meeting product specifications are available, they should be considered.

There are two typical ways that an adsorption step is scaled up: (1) slurry of loose adsorbent followed by filtration and (2) filtering the process stream through a cartridge or a filtration equipment (sparkler, Nutsche) containing the adsorbent. If the cartridge option is available, it is preferred, since the loose materials are often challenging to filter from the process stream and are difficult to clean from process equipment.

In any investigation of absorbents, there are two key criteria for absorbent selection: (1) degree of removal of the color or metal (as a function of percent loading of the adsorbent) and (2) loss of product to the adsorbent. Secondary considerations include cost of the adsorbent and availability (lead time) of the adsorbent. As a general rule, activated carbons are cheaper and more readily available compared to functionalized materials. A typical protocol for studying the adsorption unit operation is described in Example 20.2.

EXAMPLE 20.2

The final intermediate in the synthesis of an API is received from a vendor and found to have a dark brown color. The intermediate (designated compound A) is used in a laboratory run to produce API, which is found to also have a brown color. The specification for the API is off-white, so color will

TABLE 20.19 Scale-Up Factors for Distillation

Factor	In Lab	At Scale	Impact	Means to Evaluate
Time	Can vary from very short to very long, depending on ΔT (difference between boiling point temperature and jacket temperature)	Typically longer than that in the lab (hours)	Instability of the stream at elevated temperature can cause a quality issue	Establish stability by refluxing the process stream at the highest anticipated pressure, and at both extremes of composition
Vacuum control	Generally excellent	Depends on equipment, may be poor. May be difficult to achieve pressures lower than 50 mmHg	Fluctuations in vacuum = fluctuations in boiling point. Some process streams have a tendency to foam, or to "bump"	Carefully test the effect of decreased pressure on distillation
Jacket temperature	Choice of ΔT between jacket and boiling point drives distillation. Lower jacket temperatures might be adequate in the lab to achieve a reasonable distillation rate	Due to lower heat transfer area per volume, greater jacket temperatures may be desirable	Higher jacket temperatures may result in decomposition of any solids that are deposited onto the vessel walls during distillation	Assess the stability of the product at high temperature to see if high jacket temperature is an issue
Minimum volume	Often very low in terms of liters per kg of input (ability to agitate small volumes) or to use a rotary evaporator	Usually larger in terms of liters per kg of input. Some conical bottom vessels can have low minimum agitatable volumes. There may be safety issues associated with highly concentrated process streams on scale	More solvent is needed to achieve the end point as the minimum volume increases	Use the plant's minimum volume (in L/kg) in the lab study. Perform safety evaluation of concentrated process streams
End point volume	Easy to mark a volume end point on glassware	May be difficult to see volume landmarks in the vessel, radar level sensor may be present, but may not be very accurate (±5% typical, sometimes ±10%). Foaming can result in inaccurate radar measurement	If no in-process control is established (e.g., quantitation of the product concentration), the concentration going into the next unit operation may be off-target	Assess the sensitivity of downstream unit operations to variations in the concentration representing both under- and overdistillation

(*Continued*)

TABLE 20.19 (*Continued*)

Factor	In Lab	At Scale	Impact	Means to Evaluate
End point composition	In early development, the process stream may be rotovapped to an oil followed by dissolution in the next solvent. In later development, a put/take or constant volume distillation is done, and the process stream is analyzed for solvent composition by GC	Can choose between sampling the product stream for solvent composition, analyzing the distillate composition, PAT monitoring of the distillate, use product temperature as a guide, or fixed distillation protocol with no in-process control	If no in-process control is established (e.g., GC on the process stream), the composition going into the next unit operation may be off-target	Assess the sensitivity of downstream unit operations to variations in the composition representing both under- and over-distillation. Develop reliable control scheme as needed
Constant volume distillation	Usually requires full-time supervision	Usually requires full-time supervision	Constant volume distillation is usually much more solvent efficient than put/take distillation; however, the need for supervision may make it a less desirable choice	Evaluate both constant volume and put/take distillation modes
Sampling	Can draw a sample through a septum	Sampling often requires the distillation be temporarily stopped to draw the sample due to limitations on the sample temperature, or the possible need to pressurize the vessel to draw a sample	Sampling can increase cycle time	To minimize the number of samples, establish vessel landmarks, end point temperature (as a function of pressure), or if the distillation is a critical operation, PAT monitoring

TABLE 20.20 Example 20.2: Screening Results

Carbon Type	Color (by Visual Inspection)	Recovery of Compound A (%)
Carbon 1	Brown	97
Carbon 2	Brown	95
Carbon 3	Very light yellow	93
Carbon 4	Brown	98
Carbon 5	Clear	82

need to be removed. This could be done either via rework of the intermediate or as a processing step in the API step.

At the beginning of the API step, compound A is dissolved in 20 L of methanol per kg of compound A. The project team decides to pursue color removal by carbon filtration after this dissolution step.

The first step is to screen various potential adsorbents. The team has five common carbons available for scale-up. One hundred milligrams of each carbon is placed in a vial along with 4 mL of compound A solution in methanol. Since the solvent quantity in the solution is 20 L/kg (or 20 mL/g), the 4 mL solution contains 200 mg of compound A. Thus, the loading of carbon in the screening experiment is 50% (100 mg of carbon to 200 mg of compound A). The samples placed in a shaker block for 60 min, and then filtered. The color is inspected visually, and the concentration of the filtrate is analyzed by HPLC for wt%. The recovery of compound A is calculated based on the HPLC quantitation and results are shown in Table 20.20.

Carbons 3 and 5 are the only adsorbents that afford color removal. Carbon 5 results in the best color; however, too much of the desired compound is lost to the carbon. The team decides to use carbon 3 for scale-up.

Since the pilot plant will use carbon cartridges, a breakthrough study is performed in the laboratory to simulate the plant operation and to determine what carbon area is needed per liter of process stream to be decolorized. A 47 mm carbon disk is set up in a filter housing. This disk is known from vendor literature to have an effective carbon surface area of 0.0135 ft^2. A fluid reservoir is connected to a pump, which is subsequently connected to the carbon disk. Downstream from the carbon disk is a filter and a UV/Vis detector. First, methanol is flushed through the system for 20 min at 5 mL/min. Then, the feed is switched to a reservoir of 300 mL of compound A solution. UV/Vis monitoring is started, and continues until all the solution is passed through the pad. The solution that has passed through the pad is collected in 5 mL fractions. A plot of the absorbance at 310 nm versus time is presented in Figure 20.2. The color begins to breakthrough at about 30.5 min, and after 35 min the color breakthrough is increasing rapidly. Judging the breakthrough point to be 35 min, the team pools all the fractions from 20 to 35 min, and proceeds with the API chemistry. The resulting material is found to be white, so 35 min is verified to be an acceptable breakthrough point.

Given the 20 min of flush and the 5 mL/min flow rate, the breakthrough point is calculated to be 75 mL ($35 - 20$ min $= 15$ min $\times$ 5 mL/min $= 75$ mL). Given the 0.0135 ft^2 carbon area of the 47 mm pad, the carbon "life" is 5.56 L/ft^2. The flux, or flow per area, was 0.37 L/(min ft^2).

For the scale-up to 5 kg API batch, the batch volume will be 100 L at the point of dissolution. Given the life of 5.56 L/ft^2, the needed carbon area to remove color in this batch is 18 ft^2 (100 L/5.56 L/ft^2 = 18 ft^2). Based on the flux of the experiment (0.37 L/(min ft^2)), a total minimum time of 15 min is required for the operation (100 L/0.37 LPM/ft^2/18 ft^2). This could also be expressed as a flow rate of 6.7 L/min.

20.3.4 Crystallization

The objective of the crystallization operation is to isolate the product as a solid, purify by leaving impurities in the liquid

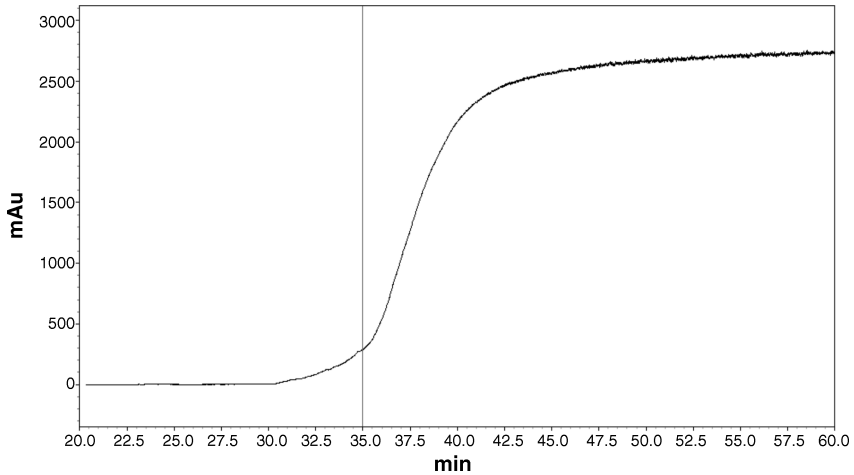


FIGURE 20.2 Carbon breakthrough curve for Example 20.2.

TABLE 20.21 Scale-Up Factors for Crystallization

Factor	In Lab	At Scale	Impact	Means to Evaluate
Metastable zone width (see text for explanation)	Generally broader	Generally narrower	Narrower metastable zone width may result in spontaneous nucleation prior to seeding, and thus uncontrolled crystallization (lack of polymorph control, lack of control of particle size distribution)	Test metastable zone width in the lab as a function of agitation, cooling rate (if applicable), and antisolvent addition rate (if applicable). Generally, to grow large particles of a desired polymorph, it is best to seed the batch under conditions of very low supersaturation [39]
Seeded/unseeded	Either is possible—easy	Either is possible—for some equipment, solids charge is difficult and the seeds are transferred as a slurry. Seed charges can be small in quantity, and it may be challenging to ensure that the seed charge reaches the batch	Polymorph control and particle size distribution control	Evaluate effect of amount of seeds (loading), seeding point, and dry versus slurry transfer
Mixing	Stir bar, or overhead stirring. Generally easy to achieve good mixing	Various agitator, vessel, and baffle configurations. For fixed equipment operated within normal volume ranges, mixing is typically good	Inadequate mixing can result in hot spots of high supersaturation, and thus uncontrolled nucleation. High agitation may reduce metastable zone width	Evaluate the impact of mixing in scale-down experiment. One means of eliminating scale dependence is by performing the mixing outside the vessel, for example, with a T-mixer or a jet mixer
Attrition	Variable	Variable	Some particles are easily broken. This process may be sensitive to agitation parameters (including time). This may affect particle size distribution, filterability, and ultimate powder properties	Explore the particle size distribution as a function of agitation using overhead stirring, or stress the process by using a high-shear mixer
Measurement of temperature	By thermocouple, not typically a problem	Temperature probes can sometimes be coated with crystals and provide false information	If jacket temperature control is used, this may not be a processing issue, but accurate temperature data will not be collected. If operating in batch temperature control mode, the control system may adjust the jacket temperature and thus move the batch temperature outside the normal operating range	Observe the tendency for coating during the crystallization. Specify jacket temperature control rather than batch temperature control

phase, and create particles of the correct form and desired physical properties (i.e., size distribution, density, surface area). As a brief review of fundamentals, crystallization consists of several physical phenomena, the most important of which are nucleation and growth (others include attrition and aggregation). Nucleation refers to the formation of very tiny crystals from the solution, and growth refers to the increase in size of the nuclei by transfer of product from the solution to the crystal faces. The balance of the rate of nucleation and growth is a key determinant of the particle size distribution. If the nucleation rate is dominant throughout the crystallization, small particles with a nonuniform distribution will form. If growth is dominant throughout the crystallization, large particles with a more monodisperse distribution will form.

Supersaturation (i.e., the state where the product concentration is above the equilibrium solubility) is required for nucleation and growth. Supersaturation is often induced by the addition of antisolvent or by lowering the batch temperature. Generally, very high supersaturation favors nucleation over growth, and low supersaturation favors growth over nucleation. In a system with no nuclei present (added seeds or foreign matter that can act as nuclei), spontaneous nucleation does not happen immediately at the onset of supersaturation. The region in the parameter space (concentration and solvent composition, or concentration and temperature) in which the solubility is exceeded but spontaneous nucleation does not occur is referred to as the metastable zone. The width of the metastable zone depends not only on the inherent characteristics of a given system but also on physical parameters such as agitation, rate of cooling or rate of antisolvent addition, and the presence of other nuclei (foreign matter or seeds). For this reason, metastable zone width depends on scale.

Table 20.21 enumerates several scale-up factors for crystallizations.

TABLE 20.22 Scale-Up Factors for Isolation

Factor	In Lab	At Scale	Impact	Means to Evaluate
Filtration flux	Up to 10× greater, depending on lab versus plant cake thickness and cake compression	Often up to 10× slower than lab, or longer	Longer cycle time	Measure filtration flux as a function of cake height or mass of cake. Use engineering correlations to predict at-scale performance (see Chapter 17)
Filter media	Typically done with filter paper, 6–25 μm	Limited choices of pore sizes and material of construction	Potential for filter media to blind or pass through of product	Evaluate plant-scale filter media in lab-scale experiments
Compressibility	Low ΔP compared to the plant, so effect of compressibility is less of a factor	Higher ΔP, so effect of compressibility is more of a factor	Can greatly slow down the filtration at high ΔP or high centrifugation spin speeds	Evaluate compressibility with leaf filter studies (pressure filtration measurements of rate versus ΔP)
Cake wash	Able to smooth cracks in the wet cake	Sometimes not able to smooth cracks in the wet cake (this can be done in a filter dryer)	Channeling of cake wash through cracks results in poor washing of the cake, affecting impurity profile and solvent content	Evaluate propensity to crack by allowing cake to deliquor completely between filtration and each wash
Extent of deliquoring	Typically easy to achieve low solvent content	Solvent content after isolation may be much greater	Greater solvent content impacts cake wash efficiency and drying operations. Stability of the product may be an issue	Study stability of wet cake under very wet conditions (e.g., 50% wash solvent)
Discharge	Easy—by scooping wet cake from Büchner funnel into a drying dish	May be challenging depending on equipment. Safety considerations such as electrostatic buildup from nonconductive washes may dictate need to delay (for relaxation of charge)	Wet cake properties needed to select appropriate parameters on equipment (i.e., peeler centrifuges—LOD, wet cake density). Longer discharge requires additional product stability under wet conditions	Study stability of wet cake under very wet conditions (e.g., 50% wash solvent)

20.3.5 Isolation

The objective of the isolation operation is to separate the solids (product or waste) from the mother liquors as rapidly as possible, and efficiently wash nondesired components (organic impurities, inorganic salts, solvents, or product) from the isolated material. Table 20.22 enumerates several scale-up factors for isolations.

20.3.6 Drying

The objective of the drying operation is to remove solvents to achieve a final product solvent specification, and to maintain or create desired powder properties. A typical drying target is set to remove solvent below a maximum allowable concentration. When drying a solvate crystalline form, minimum and maximum solvent content criteria will be set. Table 20.23 enumerates several scale-up factors for drying.

20.3.7 Particle Size Reduction (Milling)

An active pharmaceutical ingredient typically has a specification related to the powder properties. Particle size control may also be critical for process intermediate seeds to ensure sufficient impurity rejection or to improve filterability. The most common specification is related to final particle size distribution and often given as a single number that characterizes the particle size distribution. Example specifications include the mean (volume or mass based), or a D "number" (i.e., D_{50}, D_{90}, D_{97}), which refers to a value on the distribution such that "number" % (by mass) of the particles have a diameter of this value or less. Different moments of the particle size distribution as well as surface area and bulk density may also be chosen as a specification.

Development scientists can attempt to address the powder property requirement by several means, including crystallization engineering, wet milling, and dry milling. Each of these technologies is addressed in more detail elsewhere, and crystallization scale-up factors are discussed above. A requirement to make amorphous API would entail consideration of additional technologies such as spray drying. Issues related to scale-up of milling processes depend on (1) the equipment for the specific milling technology and (2) the physical properties of the compound (bulk density,

TABLE 20.23 Scale-Up Factors for Drying

Factor	In Lab	At Scale	Impact	Means to Evaluate
Agitated drying	Not always evaluated	Agitated filter dryers, rotary tumble, and conical dryers are most common drying methods. The LOD in which agitation begins is important parameter for determining powder properties	Agitation can promote lump/ball/boulder formation in cohesive powders. Agitation can influence all of the key final powder properties through breakage or attrition of particles—bulk density, particle size distribution, flowability, electrostatics	Lab-scale agitated dryer units are available. Scale-down of agitation drying experiments is not straightforward, so laboratory data may only provide trends or insights into tendencies of the system, not quantitative prediction of scale behavior
Bulk density	Easy to adapt to low bulk density	Bulk density dictates needed dryer size	Can greatly affect the choice of equipment or number of dryer loads. May affect formulation performance	See above
Sampling	Scoop/spatula	Sampling configurations differ between different dryers. The operation may be difficult, and samples may not be fully representative. Multiple samples generally taken	Too frequent sampling adversely affects cycle time. Nonrepresentative samples can result in false passing results from in-process controls	Establish tolerance for solvents/water in downstream processing (or API release). PAT methods for monitoring drying may sometimes be implemented if drying is a critical operation. PAT may be especially useful if attempting to maintain a solvate (to prevent overdrying)
Discharge	Scoop/spatula	Depends on dryer—discharge may occur through a small port and may not be trivial. Often, a significant heel is left behind after discharge	Poorly-flowing powders can be very difficult to discharge and may require excessive time/operator intervention	Measure the flow characteristics of the powder after agitated drying

TABLE 20.24 Summary of Milling Technologies

Milling Technology	Key Advantages [40]	Key Parameters and Issues for Evaluation and Scale-Up
Air attrition milling (jet or loop mills)	• Capable of attrition down to D_{97} of 2–10 μm • No heat generation—ideal for heat-sensitive compounds • Easy maintenance—no moving parts • Inert milling	• Pressures (pusher and grinding) • Mass of solids/gas flow rate ratio • Tendency of material to compact and stick to raceway surface
Fluidized bed air attrition mills with classifiers	• Capable of attrition down to D_{97} of 2–10 μm • No heat generation—ideal for heat-sensitive compounds • Steeper particle size distributions are achievable • Inert milling	• Pressure • Classifier speed • Nitrogen flow to achieve fluidization • Product feed rate/product removal rate • Pin or hammer speed • Product feed rate
Impact milling (hammer, pin)	• Capable of attrition down to D_{97} of 30–50 μm • Large industrial-scale units for very high throughput	• Sensitivity of compound to temperature
High-shear rotor–stator wet milling [41, 42]	• Capable of attrition down to 10–30 μm as a mean • Technique can be set up as a recycle of the crystallized slurry • No exposure to dry powders • More suited for "needle" morphologies to reach lower end of attrition	• Rotor–stator configuration (number of teeth, gap width) • Shear frequency, shear rate • Slurry concentration • Batch turnovers • Point of wet milling initiation during the crystallization time cycle • Product filterability
Media and ball milling	• Capable of attrition down to $D_{97} < 1$ μm • Technique can be set up as a recycle of the crystallized slurry • No exposure to dry powders	• Media size • Media material compatibility • Duration of the milling run • Product filterability

flowability, morphology, tendency for compaction, fragility). The parameters to consider for scale-up will vary with milling technology since the mechanisms for attrition are different. For milling scale-down, laboratory-sized units are available for experiments in the 10–100 g scale. While scale factors and empirical rules are used to determine the initial parameters for scaling up milling operations, a small test batch is often run to verify the physical properties (PSD, etc.) prior to milling the entire batch. PAT monitoring of the particle size distribution through online particle size analysis (Insitec, FBRM) is a prudent means of ensuring that the correct particle size is achieved. Some of the key advantages and parameters/issues to consider for the various milling technologies are described in Table 20.24.

20.4 SUMMARY

Understanding process scale-up and assessment is a core activity for process chemical engineers in the pharmaceutical industry. It enables transformation of a chemical synthesis to a scalable pilot plant process and then to a robust manufacturing process. The numerous factors to consider in the scale-up and assessment encompass addressing the specific risks to safety, quality, and manufacturing productivity as well as the more general strategic risks in managing a portfolio of projects that span different stages of development. In this chapter, we have discussed many drivers for development, including the requisite process and personnel safety, product quality, and business optimization. Understanding these drivers is the key to both efficiently prioritizing development activities for a given project's stage of development and ensuring that resources are appropriately prioritized across the portfolio. We have also discussed the unit operations that constitute a typical process. Understanding of the process fit and scale-up factors for these unit operations is critical to defining and executing a process development strategy. By applying these concepts, along with more detailed insights from the other chapters in this book, the process engineer will be well-prepared to meet the challenges of API process development.

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