development scientist must keep in mind that the scale of the process may influence results. For example, it is commonly assumed that development of the freeze-drying cycle changes greatly on going from lab scale to pilot scale to production scale. Ideally, experiments can be performed at pilot scale using equipment representative of the production process. In addition, the sequence of steps in the process, acceptable environmental conditions (temperature, humidity, air, etc.) for the unit operation, and acceptable excipient ranges should be evaluated.

For solutions, the following process conditions may impact product quality:

1. *Agitation* (rate, duration): High rates may result in undesired foaming, denaturation, aggregation, or oxidation. Kim *et al.* (1994) reported on the effect of high shear force on the α helix-to-β sheet conversion of insulinotropin resulting in a reduced solubility of the protein. Thus, agitation or mixing rates will affect the conformation and solubility of this protein, thus requiring special control of these rates.
2. *Compounding sequence:* Order of addition of excipients and drug substance must be determined. Normally, excipients are added and dissolved before drug substance is added (Harwood *et al.*, 1993). This allows sufficient time for excipients to dissolve while minimizing time in solution for unstable drug substances.
3. *pH adjustments:* Prolonged exposure to acid or basic pHs can cause protein degradation.
4. *Filtration:* A membrane is selected which offers low protein binding as confirmed by protein assays on the solutions before and after filtration to detect any losses (Hawker and Hawker, 1975). This is discussed in detail in Chapter 5.
5. *Filtration and filling:* The temperature may need to be controlled to prevent chemical degradation during filling. Rates of filtration and filling should be considered to prevent shearing of the protein, although this possibility is remote. Effects of filtration and filling rates were studied for human growth hormone (Hsu *et al.*, 1988; Pikal *et al.*, 1991b). Shear forces encountered during processing were found not to cause aggregation of human growth hormone. However, aggregation of proteins during filtration and filling can be caused by interactions of the protein with polymeric hydrophobic surfaces, such as those composing sterilizing filters and process tubing for filling equipment, suspected to be the cause of human growth hormone aggregation during processing (Hsu *et al.*, 1988).

Insulin aggregation and fibrillation can be caused by interaction of the protein in solution with plastics (Thurow and Geisen, 1984) (see previous discussion on insulin binding to plastic surfaces).

6. *Freeze-drying:* Denaturation of a protein solution may occur because of pH shifts or ionic strength changes during freezing (Orii and Morita, 1977). The freezing rate, concentration, endpoint pH, and time and temperature of holding prior to lyophilization may affect the chemical and physical stability of the product (see Chapter 6).
7. *Environmental conditions:* Sparging of nitrogen into solution to remove dissolved gases or use of a nitrogen overlay to replace the air headspace during filling to retard the oxidation of oxygen-labile formulation may be required (Brown and Leeson, 1969).
8. *Materials compatibility:* During the manufacture, the drug is exposed to various materials such as stainless steel, filters, tubing, and pump diaphragms. It is important to ensure that the formulation components are compatible with these materials.
9. *Time and temperature:* Throughout manufacture, critical holding times and temperatures need to be established, not only for protein stability protection purposes, but also to assure microbiological control, particularly to prevent endotoxin contamination.

See Chapter 7 on quality assurance and quality control for additional details on this topic.

12.3. Clinical Trial Supplies

As the transfer of a process from laboratory scale into the clinical phase occurs, the development scientist needs to be involved during the early production of clinical trial supplies as well as during any subsequent formulation and process changes. The development scientist can obtain valuable insight into the conditions of manufacturing as well as provide key input to the manufacturing groups about the rationale for formulation and process decisions. These lots also provide an opportunity to collect information under larger scale manufacturing conditions than in laboratory-scale experiments. In-process testing should be routinely conducted during the manufacture of clinical supplies. The data are used to evaluate the process and lead to process improvements, which ultimately support the transfer into the manufacturing phase at full scale.

13. QUALITY CONSIDERATIONS DURING FORMULATION DEVELOPMENT

13.1. Early Product Assessment

All known physical and chemical properties of a protein should be viewed in light of how these properties will affect final quality of the finished dosage form. The development scientist should build quality into the process so that it can be validated and data exist to support "worst-case" limits (e.g., extremes in pH, excipient levels, time/temperature limits). Process design should be evaluated to assure control of quality parameters.

13.2. Documentation

An essential element of validation is establishing thorough documentation that a process will consistently meet its predetermined specifications and quality attributes. Ongoing documentation is essential during formulation development. Development history reports are required during preapproval inspections and are generally a high-level overview describing the history of the drug product from preliminary studies to the commercial formulation and the process submitted in the regulatory document. There may be one report or several to describe the various steps of development (e.g., fermentation, granule isolation, drug substance, drug product, methods development). It is as important to document what did not work as what worked and why decisions were made. Where necessary, bioequivalence of lots used in clinical trials should be demonstrated. A method history report should contain information on regulatory commitments during the development process and give the history of each method. Rationale for specifications, reference standards, and cleaning methods should be provided. For product development reports, lot rejections, deviations, and resolution of the issues need to be covered. Typical contents of a parenteral drug product development history report include the following:

- Preformulation data
- Selection of excipients supported by preformulation studies
- Antimicrobial characteristics of the product
- Rationale and basis for packaging component choices
- Description of container/closure integrity studies

- Overview of the manufacturing process with a description of each unit operation, acceptance criteria for all critical steps of the process, and a history of results for each step
- Scale-up studies
- Stability overview, including product use studies

Development history reports include, but are not limited to, method histories, formulation, primary packaging, process development, and control strategy.

Technical reports prepared on an ongoing basis aid in compiling the development history reports and are key in the information transfer to the manufacturing sites. Typical information contained in these periodic reports are the rationale for decisions, description of what worked and what did not work, and information for solving manufacturing problems.

13.3. Stability Studies

Stability testing of protein and peptide dosage forms should follow the ICH guidelines (U.S. FDA, 1996; ICH, 1995). Table XVI summarizes the requirements of this guideline. Three batches or more of the final product in the final container/closure system that represents the finished product manufacturing scale must be put on stability testing. The batches should use different lots of bulk material. A minimum of 6 months of data at desired storage conditions must be available at the time of submission (less than 6 months of data for products that will have less than 6 months dating). Product expiration dating is based on real-time data, not extrapolated from accelerated stability studies. If different volumes and/or strengths of the same formulation are to be tested, a matrix system or bracketing may be permitted. Details of matrixing and bracketing are found in the guideline.

Stability testing must use methods that are stability-indicating and validated. Methods should monitor changes in potency, purity, and other product characteristics* as a function of time and storage conditions as defined in the stability protocol. Data on final product in containers maintained in an inverted or horizontal position and all different container/closure combinations must be obtained. Multiple dose containers must have data to support stability during simulated use, for example, repeated

*Visual appearance, visible particulates in solutions. pH, moisture level of powders, sterility testing or container/closure integrity, degradation, if any, of additives.

Table XVI
Summary of Guideline for Stability Testing of Biotechnological and Biological Products[a]

Selection of batches	Guidance for stability studies for regulatory submissions
A. Drug substance	At least three batches representative of production scale
	A minimum of 6 months of stability data at time of submission (unless storage period will be less than 6 months)
	Pilot-plant-scale batch data acceptable at submission as long as there is commitment to place first three manufacturing-scale batches into long-term stability program after approval
	Storage containers should represent actual holding containers to be used during manufacture; containers of reduced size acceptable, provided they are constructed of same material and use same type of container/closure system
B. Intermediates	Identify intermediates and generate in-house data and process limits to assure final product stability
C. Drug product	At least three batches of final container product representative of final product at production scale
	Different batches of bulk material should be studied in final product
	A minimum of 6 months of data at time of submission (unless storage period will be less than 6 months)
	Product expiration dating based on real-time/real-temperature data
	Continuing stability updates should occur during review process
	Quality of final product must be representative of quality of material used in clinical studies
	Pilot-plant-scale batch data acceptable at submission as long as there is commitment to place first three manufacturing scale batches into long-term stability program after approval
D. Sample selection	Matrix system and/or bracketing is acceptable when product consists of different fill volumes, units, or mass

Stability-indicating profile	Guidance
A. Protocol	Include detailed protocol for assessment of stability of both bulk drug substance and drug product to support proposed storage conditions and expiration dating periods; include statistical methods, specifications, test intervals
B. Potency	Potency must be compared to an appropriate reference standard
	Perform at appropriate intervals as defined in the protocol and report in units of biological activity calibrated against some recognized standard
C. Purity/molecular characteristics	Purity should be assessed by more than one method
	Limits of acceptable degradation should be documented and justified, taking into account levels observed in material used in preclinical and clinical studies
	Usual methods include electrophoresis, high-resolution chromatography, and peptide mapping

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.