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REVIEW

Drug Product Development: A Technical Review of Chemistry, Manufacturing, and Controls Information for the Support of Pharmaceutical Compound Licensing Activities

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INTRODUCTION

Due diligence is a vital activity in the acquisition or the in-licensing of pharmaceutical compounds for market commercialization. Pharmaceutical product due diligence is a detailed investigation of the chemistry, manufacturing, and controls (CMC) information associated with a drug product. The investigation provides assurance that a given compound will meet the requisite technical and quality elements to allow for successful commercialization of the drug product. This document provides an overview of the CMC information that is reviewed as part of the drug product due diligence activities. This review follows the format of the Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use: Module 3, Quality, of the ICH Harmonised Tripartite Guideline[1] with some sections of the CTD template combined to simplify the presentation. A drug substance overview is given elsewhere.[2]

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

The assessment begins with a review of the formulation. The components of the formulation are categorized according to their function. The drug product is categorized according to its route of administration. A description of the drug product qualitative/quantitative composition provides a list of all ingredients, including solvents used in the manufacture of the drug product. The functional aspects of each component of the drug product are central to the development rationalization of the formulation and serve as reference points in the examination of supportive development data. An understanding of

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each component's function allows for data-driven risk assessment during the due diligence investigation.

The functional aspects of excipients can be divided into four basic categories that may impact (1) stability of the drug substance, (2) physical characteristics, (3) in vivo absorption, and (4) manufacturability.[3] While these general classifications can be applied, excipients may have multifunctional roles, and, thus, the degree of physical characterization of the excipient is dependent upon complete elucidation of the excipient function. For example, hydroxypropyl methylcellulose (HPMC) commonly is used as a tablet binder for solid oral dosage forms but also has been reported to behave as a functional inhibitor of hydrate formation of a drug substance.[4] The degree of characterization and control of the excipient in this instance would be contingent, in part, upon those physicochemical aspects of the HPMC that inhibit the drug substance hydrate formation. Figure 1 depicts the role of the excipients in supporting the performance of the drug product.

Excipient Impact on Stability

From the above example, it is seen that excipients may be used as stabilizing agents.[5] Moisture-induced degradation commonly is associated with dosage forms and may entail simple hydrolysis, or, in some cases, water may serve as a plastisizer to increase molecular mobility and, hence, reactivity of the drug substance.[6] It has been postulated that excipients with a strong affinity for water may function to keep water away from the active drug substance and prevent moisture-induced degradation. However, excessive moisture uptake by the excipient may, in contrast, facilitate degradation of the active ingredient.[7] Oxidative degradation is another common form of degradation. Additives such as butylated hydroxyanisole and ascorbic acid have been used to stabilize formulations against oxidation.[5] Excipients also have been used in model formulations to stabilize photosensitive compounds.[8]

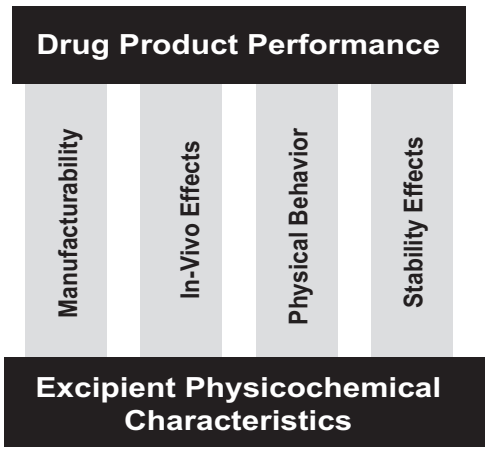

Figure 1. The excipient physicochemical characteristics provide the foundation for overall drug product performance.

Physical Roles of Excipients

Excipients play practical physical roles in dosage forms, serving as diluents to allow formulation of appropriately sized tablets, disintegrants to enhance formulation disintegration, and coatings to protect the tablet or mask undesirable organoleptic qualities of the drug substance.

In Vivo Effects of Excipients

Excipients have the potential to impact the in vivo absorption of drugs. The factors that may influence bioavailability include the in vivo disintegration and dissolution of the dosage form and the excipient influence on physiological processes and factors such as pH of the microenvironment, gastrointestinal tract (GI) transit time, and stability of the drug substance in the GI tract.[9] For example, the impact of cyclodextrins on in vivo drug delivery indicates that, for hydrophobic drugs with dissolution rate limited absorption, improved bioavailability may be derived by the presence of cyclodextrin derivatives.[10] The potential impact of excipients is thus related, in part, to the solubility and permeability characteristics of the drug substance.[11,12] A detailed understanding of the drug substance's physicochemical characteristics is essential to the elucidation of the functional role of the dosage form excipients.

Excipients in the Manufacturing Process

The manufacturability of the dosage form is exemplified in the use of magnesium stearate as a lubricant to allow for successful tablet compression.[13] Other examples of drug/excipient interactions have been well documented.[14] The requisite excipient

specifications, therefore, are derived from the level of control necessary to assure that the excipient meets the quality attributes related to their function. Preformulation study data allow the due diligence reviewer to confirm the assignment of the critical quality attributes of the excipient relative to the excipient's purported role in dosage form functionality. The data should demonstrate, through controlled experiments, the functional role of the excipient and any physicochemical characteristics of the excipient critical to its function in the formulation.

PHARMACEUTICAL DEVELOPMENT

Formulations can be categorized according to the route of administration and include oral, rectal, vaginal, inhalation, topical, transdermal, intraocular, intranasal, and parenteral drug products.[15] The discussion here will be generalized to cover solid and liquid (including parenteral) formulations. This generalized approach provides information pertinent to preformulation applications for most dosage forms.

Pharmaceutical development information provides the scientific rationale for the formulation development approach through to the final development and justification of a suitable dosage form. Regulatory guidance describes only limited detail of the requirements for the data sets associated with pharmaceutical development.[16,17] Although more detailed guidance is available for the toxicological assessment of excipients,[18] the detailed scientific approach to formulation development and justification is left to the discretion of the development organization, and the level of detail is dependent upon the complexity of the dosage form. The outline below provides an overview of some of the requisite studies associated with formulation development. The due diligence review should assess the availability of formulation development study data, with an emphasis on potential interactions between the drug substance and excipients that could impact dosage form behavior.

Components of the Drug Product

Drug Substance

Drug substance characterization is discussed elsewhere.[2] The properties of the drug substance can have a significant effect on the physical and chemical behavior of the drug product. A review of the drug substance physical and chemical properties is performed in relation to the excipient characteristics. For example, particle shape of the drug substance can impact the bulk properties of a drug product powder and can influence flow properties of the drug/excipient blend in the manufacturing process.[19] The ultimate influence of the drug substance particle characteristics on drug product performance will depend, in part, on the characteristics of the excipients.

Excipients

Excipients typically are the major fraction of the solid dosage form. As such, the characterization of the individual drug/excipient interaction is an important part of understanding the overall behavior of the dosage form. It is well known from studies of drug substances that water associated with the drug substance solid can influence chemical degradation rates, dissolution, powder flow, and other physical properties.[20] Likewise, the physical state of the excipient can impact the performance of the drug product. The regulatory status of the excipient is an additional consideration. In the United States, an excipient that is ''generally recognized as safe,'' (GRAS) for it's intended use can be exempted from premarket approval requirements of the Federal Food, Drug, and Cosmetic Act.[21] In Europe, noncompendial excipients must meet food additive requirements.[22] Are the excipients well characterized with regard to safety? If the excipients are not GRAS or do not have food additive status, have the excipients been used in approved products in the United States or Europe? Is the use of this excipient in pharmaceutical products documented in the literature? In the absence of such information, the safety profile of the excipient must be demonstrated, thereby adding an additional regulatory burden.[18]

The source of excipients used in the drug product should be considered. A general compendial guidance, such as the United States Pharmacopeia (USP), recommends that suppliers of excipients meet current good manufacturing practices (cGMP) requirements. If the supplier has not received a cGMP inspection by a regulatory body, an in-house quality inspection of the facility should be performed as part of the due diligence investigation. Adequate control during the excipient manufacturing process provides increased certainty that the quality attributes of the excipient determined to be critical

will continue to be met. While the manufacturer can assure meeting the compendial requirements of the excipient, it is not possible for the monograph to include every possible impurity (considering that monograph substances may be prepared by various methods of manufacture). It is, therefore, important for the source of the excipient to be controlled and the quality of the material to be characterized beyond basic compendial requirements to include those critical quality attributes (CQA) that impact the drug product performance. What is the synthetic route of the excipient? What are common impurities of the process? Are the impurities characterized? How does the manufacturer control these impurities? Do these impurities have chemical characteristics that would indicate the potential for interaction with the drug substance? What are the physical characteristics of the excipient (e.g., shape, size)?

Solid Dosage Forms

Solid-state reactions in the dosage form can occur when the drug substance intrinsically is reactive and may be accelerated by interaction with excipients (chemical/physical interaction) or induced by excipients (where the excipient does not chemically interact but promotes the degradation of the drug substance).[23] Some incompatibilities of drug substance functional groups and excipients are documented in the literature and can provide guidance in the design phase of compatibility studies. For example, primary and secondary amines can react with reducing agents (e.g., lactose, glucose, and maltose) to form glycosylamines.[24,25] An alternative to reducing sugars is the use of nonreducing carbohydrates such as mannitol and sucrose. The due diligence analysis should include a review of the fundamental chemistry of the drug substance and the excipients. Are any potential incompatibilities apparent?

Two common techniques to examine drug/excipient compatibility are differential scanning calorimetry (DSC) and chromatographic analysis.[26] Differential scanning calorimetry detects interactions that are accompanied by a change in heat. These interactions include chemical degradation, melting, and mixing.[27] Chromatographic analysis of drug/excipient mixes placed under accelerated storage is a complementary technique that determines the potential formation of degradation species over time. As a first approach to drug/excipient compatibility, the use of DSC is evident throughout the literature.[28–30] The advantages of DSC trials include the small amounts of material necessary for the study and the facile nature of the technique. In addition to DSC, thermogravimetric analysis (TGA) offers a complementary view of potential incompatibilities. Small weight changes due to chemical reactions can be readily distinguished from thermal changes that occur without weight changes (melting, crystallization, or polymorphic changes).[20] Traditionally, 50/50 (w/w) mixtures of the drug and the excipient are tested. Ranges of drug/excipient ratios also should be tested, since interactions may be concentration dependent.[31] More recent studies that use high-sensitivity DSC[32] and isothermal microcalorimetry[33] suggest that the intentional incorporation of water into the sample may provide information regarding the moisture sensitivity of the product. After initial binary studies are performed, similar studies can be performed on tertiary or higher order mixtures, although the interpretation of such data can be difficult due to the potential complexity of the interactions.

Other techniques such as Fourier transform infrared analysis (FTIR) spectroscopy, x-ray powder diffraction, and liquid chromatography–tandem mass spectrometry (LC–MS/MS) analysis also have been used to investigate drug/excipient compatibility.[14,34] For example, infrared (IR) studies of amoxicillin trihydrate in ethyl cellulose granules suggested hydrogen bonding between the excipient and the active ingredient.[35] The application of complementary techniques is useful in determining the extent and nature of interactions between the drug substance and the excipients. Compounds in early preclinical development will have limited stability data. Compatibility information provides a means to predict the potential challenges that may be faced as clinical development proceeds.

After the initial screening of excipients is completed, short-term, accelerated stability studies of model formulations are performed. These studies entail the mixing a drug with excipients and the storage of samples at an elevated temperature and humidity. In order to accentuate any potential incompatibilities, different mixing procedures are used, such as mixing with a spatula, grinding of components separately with a mortar and pestle prior to mixing or grinding the components together with a mortar and pestle.[28] Typically, the analysis is performed by using multiple chromatographic methods or a gradient high-performance liquid chromatography method, since fully validated methods are not normally available in the early stages of development.[18] The use of multiple procedures or gradient elution helps to assure that unidentified degradation products will be observed if present.

Analysis of compatibility studies requires careful interpretation of the data as demonstrated in studies of polyvinylpyrrolidone (PVP) with a pharmaceutical drug substance.[36] In this example, exposure of the drug product to an elevated temperature and humidity (40°C/75% relative humidity) resulted in the physical change of the excipient from the glassy to the rubbery state (the glass transition state change is noted by a change in the specific heat capacity of the material[37] resulting in a loss of pore structure of the solid mix and a concomitant decrease in the dissolution rate. This effect is not seen in long-term studies at 30°C/60% RH (below the glass transition temperature for PVP). Thus, the results of thermal methods or elevated temperature and humidity studies to explore compatibility may not be predictive, necessarily, of the long-term behavior of the dosage form but can provide, ultimately, a useful data set in understanding the nature of the drug/excipient interaction. Table 1 summarizes the utility of some of the analytical techniques used to characterize drug/excipient compatibility.

Subsequent to compatibility studies, prototype formulations can be made and tested for physical and chemical performance. Consistent with the ultimate regulatory requirements of solid dosage forms,[38] multiple aspects of performance are examined, including dissolution, disintegration, hardness, friability, assay, and purity profile.

Liquid Dosage Forms

Liquid formulations span a variety of dosage forms, including oral liquids and parenteral formulations. The discussion here includes parenteral formulations as an example of liquid dosage forms since the requirements for oral liquids may be considered a subset of the requirements of liquid parenterals. A review of commonly used excipients in approved parenteral products has been compiled and classifies excipients into seven categories based upon their function.[39,40] The excipients are categorized as solvents, thickening agents, chelating agents, antioxidants (including reducing agents and antioxidant synergists), preservatives, buffers, and bulking agents. The compiled list represents a starting point to examine potential compatibility of the parenteral drug substance with commonly used excipients and may be applicable to other liquid products such as oral liquid formulations.

For liquid formulations, the compatibility study of the drug/excipient mixture with the packaging system is an essential activity due to the intimate contact between the product and the container.[41] For powder-fill systems, an approach similar to that of solid-dosage systems is taken with regard to compatibility testing, albeit in the presence of the proposed packaging system. In addition, products for reconstitution must demonstrate adequate compatibility with proposed diluents. For parenteral liquids, admixing with lactated ringer's injection, 5% weight/volume (w/v), dextrose injection, and 0.9% w/v sodium chloride injection solutions should be studied.

One of the first determinations made for liquid formulations is the affect of pH on the stability of the solution.[42] Chemical and physical stability is studied over a range of pH values. The first pass analysis entails an examination for the presence of any precipitate forming over time. Samples are

Table 1. Drug substance/excipient compatibility testing—techniques and the utility of the information derived.

Investigative technique	Measurement	Utility of data
DSC	Energy is absorbed or released by a sample as it is heated, cooled, or held at a constant temperature	Physicochemical compatibility of drug and excipients
TGA	Weight changes by a sample as it is heated, cooled, or held at a constant temperature	Physicochemical compatibility of drug and excipients
Chromatographic analysis	Chemical interactions of the sample with the stationary phase and the mobile phase	Excipients, drug product purity; excipient–drug substance chemical compatibility
Microcalorimetry	Absorbance or release of heat from solution sample	Physicochemical compatibility of drug and excipients; solution applications
X-ray diffraction	Scattering of x-ray radiation by a solid sample	Polymorph characterization
Microscopy	Magnified appearance of sample	Particle size, morphology
LC-MS/MS	Chromatographic separation and fragmentation of molecular species	Impurity, degradation product identification

stored refrigerated and at elevated temperatures. Based upon the results of the pH-range studies, cosolvents can be added to the formulation to enhance the solubility of the drug. As the obvious physical failures are identified, more specific tests for particulates can be performed by using techniques such as particle counting with laser diffraction. Due to the complexity of particulate formation in solutions, longer-term studies in the proposed container at the recommended storage temperature can prevent predictive failures by using accelerated temperature techniques. For example, a study of minodronic acid injectable at an elevated temperature (60°C), in glass vials, indicated no particulate formation after 3 months of storage. However, studies at 25°C demonstrated particulate formation.[43] Data indicated an aluminum–minodronic acid complex and it was hypothesized that the complex formation was exothermic, resulting in thermodynamically unfavorable conditions for complex formation at elevated conditions. The challenge of the due diligence review is placing each data set in proper perspective with regard to the data's predictability of drug development success.

Buffering agents are added to formulations where pH control is important for stability or administration of the dosage form. For lyophilized products, the relevance of pH stability is particularly important with regard to pH changes induced by salt precipitation of buffer components during the far-from-equilibrium freezing that occurs during the lyophilization process.[44] The complex nature of the nonequilibrium freezing can be impacted by the solution composition and the freezing rate. A review of the development of the lyophilization process, as outlined later, includes study of the impact of processing parameters on the quality of the lyophilized cake.

The solution behavior of the drug substance also may be influenced by the propensity of the molecular solution species to form aggregates (e.g., dimers, trimers or higher-order micellar systems). One technique that has been used successfully to study noncovalent molecular associations of solution species is electrospray ionization mass spectrometry.[45] The technique provides sufficient ion desolvation, while preserving the noncovalent interactions of the solution species. The self-association of drug solute species can influence the solution stability of the drug substance.[46] The determination of the nature of the aggregation (i.e., micelle formation vs. low-order association) may be relevant to understanding the solution stability behavior of the drug substance, since association may be affected by the presence of other excipients. The impact of molecular association is apparent in the concentration dependency of solution stability for some liquid drug products.

The impact of oxygen on the formulation is examined because some drug substances are oxygen sensitive.[47] Oxygen sensitive compounds may need an inert atmosphere in the package headspace. If the stability of the formulation is effected by the presence of oxygen, analytical data should be available indicating the extent of the sensitivity (i.e., the kinetic rate of degradation) and the ability of controlled environmental-processing conditions to provide adequate stability.

For sterile liquid dosage formulations, the stability of the formulation when autoclaved is an important consideration with regulatory implications. Products that are intended to be sterile should be sterilized in their final container with the preference being moist heat at 121°C for 15 min.[48] More passive techniques of sterilization, such as sterile filtration, are pursued only if the drug product is incompatible with heat sterilization. Well-documented development efforts are essential to defending the need for a formulation that cannot undergo heat sterilization. For nonsterile liquids, assurance of acceptable microbial bioburden during manufacture and throughout shelf life should be demonstrated. As with other excipients, the physical and chemical compatibility of the preservative or antioxidant should be demonstrated. In addition, the level of antioxidant or preservative should be justified with regard to safety. The minimum concentration of preservative should be used that produces the required level of efficacy. Some preservatives should be avoided such as those containing mercury (thimerosal); sulphites and metabisulphites; benzyl alcohol, when used in pediatric formulations for children under the age of two, and benzoic acid esters in parenterals.[49]

Suspension formulations may be developed when the drug substance has inadequate solubility to be formulated as a solution or if the suspension of the drug is more stable than the solution of the drug substance. Some of the characteristics of acceptable suspensions (beyond requisite stability requirements) include nonrapid settling of particles (sedimentation), resuspendibility, and homogeneity of resuspended mixtures.[50] These physical aspects of the formulation may be influenced by the particle concentration, charge, shape, and size, as well as the specific gravity and viscosity of the suspension.[51]

Particle size of the drug substance in the suspension is an important aspect of the formulation. Comparative bioavailability of sterile suspensions

with different particle size ranges has demonstrated bioinequivalence.[52] The importance of the drug substance particle size has led to specialized techniques to produce specific particle size ranges, including ranges to support nanoparticle suspensions.[53] In addition to control of the drug substance particle size prior to formulation, the control of the particle size in the suspension must account for potential for Ostwald ripening, whereby particles grow in the suspension over time. It has been suggested that the key factor in reducing crystal growth in a suspension is to lower the interfacial tension between the solid and liquid.[54] The reduction in interfacial tension can be accomplished by the addition of surfactants and hydrophobic excipients, and has been demonstrated for a series of emulsions.[55,56] Examination of adsorption of the surfactant to the drug substance particles may be useful in the development of physically stable formulations. In addition to bioavailability considerations, sterile suspensions for injection require specific physical attributes to provide effective syringeability and injectability.[57] Table 2 provides a checklist for due diligence drug product review of the description and the composition of the drug product, and pharmaceutical development and drug substance/excipient compatibility for solid dosage forms.

Table 2. A summary checklist of key CMC review aspects of drug product— description and composition the drug product; pharmaceutical development and drug substance/excipient compatibility for solid dosage forms.

Description and composition of the drug product
Qualitative/quantitative description
Excipient function defined
Excipient stability effect
Excipient physical role
Excipient in vivo absorption effect
Excipient manufacturability effect
Pharmaceutical Development
Drug substance characterized
Excipients
GRAS status (21 CFR Part 170.3)
Compendial status of excipient
Food grade status of excipient (Council Directive 89/107/EEC)
Supplier cGMP status
Supplier internal audit results
Excipient used in any approved products in EU or U.S.
Use of excipient in pharmaceutical product documented in literature
Safety profile of excipient
Synthetic route of excipient identified
If compendial, are all excipient impurities controlled by monograph?
Excipient impurities characterized (potential for interaction)
Manufacturer control of excipient impurities
Drug substance/excipient compatibility (solid dosage forms)
Analytical techniques
Differential scanning calorimetry (DSC)
Chromatographic analysis
Thermal gravimetric analysis (TGA)
Microcalorimetry
Fourier transform infrared analysis (FTIR)
X-ray diffraction
Microscopy
Liquid chromatography-tandem mass spectrometry (LC-MS/MS)
Drug/excipient compatibility
Drug/excipient mixing studies (thermal analysis)
Short-term accelerated stability
Multiple analysis techniques used for accelerated studies
Effect of water on compatibility

Excipient Characterization and Critical Quality Attributes

The view of functionality as a critical aspect in determining excipient quality has been amply argued and demonstrated in the literature.[3,58,59] Adequate characterization of the critical quality attributes of selected excipients is crucial to the formulation development process. The identification of critical physicochemical characteristics via compatibility studies allows for the development of methodologies to control those aspects of the excipient that are critical to product performance. The due diligence reviewer examines the data generated during preformulation studies to assess the validity of the conclusions regarding the assignment of CQAs to the excipient components.

The solid-state characteristics of excipients used in solid dosage forms should be well defined. The level of characterization and control of various physicochemical aspects of the excipient is dependent upon the outcome of the preformulation studies. For example, in some formulations, the moisture content of excipients can affect the tensile strength of tablets.[60]

The crystal form of the excipient may impact drug product performance as demonstrated with D-mannitol, where the tableting behavior as reflected in the compressibility (reduction in volume as a function of pressure), compactibility (tensile strength

as a function of compression pressure), and friction of the compacts (ejection force of the tablet from the dye as a function of the compression pressure) each show crystal form dependencies.[61]

The potential impact of particle size is amply demonstrated in a study of magnesium stearate. Magnesium stearate commonly is used as a lubricant in tablet production and its effective lubricity can be correlated to tablet ejection forces. A comparative study demonstrated that magnesium stearate batches with a smaller particle size distribution and larger surface area produces increased lubricity when compared with batches of similar quality but larger particle size and smaller surface area.[11] The flowability of the excipient or the drug/excipient mixture also can be influenced by particle size, as well as the particle shape of the excipient.[62] Characterization of excipient solid-state properties is well documented in the literature[63,64] and may entail measurements such as sieve analysis, angle of repose, and tapped and bulk density (Carr's index).

The chemical characteristics of excipients can influence drug product behavior. For example, trace impurities found in excipients can play a role in the stability of formulations. Impurities in excipients have been shown to be responsible for oxidative degradation of drug products.[65] The addition of PVP during development of an injectable formulation revealed that trace peroxides in the PVP caused oxidation of the drug substance.[66] Careful examination of the impurity profile of the excipient and its potential impact on formulation stability must be performed. Many compendial monographs do not include impurity profiles and, therefore, conformance to compendial requirements may not be sufficient for adequate characterization of the excipient.[67]

Beyond chromatographic analysis of excipients, excipient characterization can be approached by using a variety of spectroscopic techniques, including IR, near-IR, and Raman spectroscopy.[68] For example, IR and Raman analyses have been used to examine the crystallinity of hydroxypropylcellulose.[69] Volatile impurities (e.g., residual solvents) can be identified by using the thermal-spectroscopic technique of TG-IR.[65] Residual solvents may be an important feature regarding the performance of the drug product, especially with regard to dosage forms formulated with copolymers.[70] Residual solvents can increase the permeability of the coating, leading to unfavorable changes in the release profile of the drug product.

Definition of the critical quality attributes of the excipient and the drug substance will enable the implementation of appropriate controls as manufacturing process development proceeds. The due diligence review should assure that the critical quality attributes of each excipient are well defined. Preformulation data should support the selection of each CQA and its potential impact on drug product performance. Table 3 provides a checklist for due diligence drug product review of the drug/excipient compatibility (liquid dosage forms) and the excipient critical quality attributes.

Table 3. A summary checklist of key CMC review aspects of drug product—drug/excipient compatibility (liquid dosage forms) and excipient critical quality attributes.

Drug/excipient compatibility (liquid dosage forms)
pH stability
Cosolvents
Particulates
Buffering agents
Effect of aggregation
Effect of oxygen
Thermal stability
Sterile dosage forms
Suspension characteristics
Sedimentation
Resuspendibility
Homogeneity
Particle size effects
Anitmicrobial additives
Lyophilization products
Freeze drying parameters
Buffer components
Diluent compatibility
Sterilization technique
Heat sterilization data
Preservative studies
Excipient critical quality attributes
Moisture content
Crystallinity (polymorphism)
Compressibility
Compactibility
Friction of compact
Particle size
Surface area
Flowability
Morphology (particle shape/habit)
Impurity profile
Residual solvents

Manufacturing Process Development

Subsequent to the characterization of the drug substance, the excipients, and their interaction

potential, manufacturing process development can proceed. Manufacturing process development begins at the small scale and proceeds to a minimum of 10% full production scale for pivotal clinical studies and registration stability studies. Ultimately full-scale production batches (sometimes referred to as demonstration or engineering batches) are made prior to validation of the process.

A review of the manufacturing process development should include an emphasis on the reproducibility of the critical quality attributes of the drug product. Changes to the method of manufacture should be detailed as the process moved from initial phase 1 studies through to the final commercial process. The review should focus on any process changes made subsequent to the first clinical study. A review of all clinical studies and the manufacturing process used to provide the clinical supplies should be given.

The development studies should clearly detail the effect of process changes on critical quality attributes associated with the intermediates and the finished product. There are a variety of multivariate methods that can be used in process development studies.[71] The experimental designs rely on a thorough understanding of the process and its critical attributes. One approach is to follow the hazard analysis and critical control points system for identifying and controlling critical process steps.[72] Instrumental in a successful process development is to link each critical process step to a critical quality attribute. The typical industry standard in applying critical quality attributes to specific test outcomes is contingent upon the impact of the critical process step to measurable quality aspects of the final product.[73] Reworking of a drug product should include a detailed analysis of the impact on the drug product critical attributes. Reworking of tablets, for example, can have an impact on formulation flowability, tablet crushing strength, and disintegrations times.[74] The rework process should be described in detail with proposed manufacturing batch documents.

For sterile products, a review of the presterilization bioburden data should be performed because this is essential to demonstrate the ruggedness of the process.[75] For nonsterile liquid products, a review of the microbial limits testing data is performed. For components in contact with liquid products during manufacture, compatibility data should demonstrate no deleterious effects to the product quality (e.g., drug adsorption onto processing filters or tubing) or unacceptable extractable components.[76] Depending upon the phase of development, a cleaning validation protocol or report may be available for review.

Whether the drug product is a tablet manufactured via a simple direct compression process or a lyo product manufactured through a complex, multistep process, the knowledge and the control of critical process parameters is fundamental to demonstrating a well-controlled, robust process. For the direct compression tablet, the flow behavior of the formulation prior to tableting is an essential characteristic that will impact the control and selection of ranges of process parameters. Parameters of importance to the direct compression process may include mixing/blending time, order of addition of excipients, and flow rates of the blend to the tableting press. The impact of water absorption by the powder[77] during manufacture may require special humidity controls in the manufacturing facility. For a lyo product, the parameters that control the lyophilization should be defined, including the impact of deviating from the set points for critical operations. A detailed discussion of the cycle optimization should be given.[78] Data such as water vapor pressure time profiles for the lyophilization process can be used to determine the appropriateness of the defined cycles for primary and secondary drying. Ultimately, the design process can be determined as successful only with predefined quality requirements and a developed testing plan.[79]

Container Closure System

Based upon the knowledge of the physical and chemical behavior of the drug product in preformulation and subsequent stability studies of model formulations, an appropriate package is selected. For stable products with no sensitivity to environmental conditions (e.g., moisture or oxygen) the justification of the package requires data sufficient to show the acceptability of the drug product's physicochemical attributes during storage. For oxygen- or moisture-sensitive products, a package that provides an effective barrier must be demonstrated. In addition, it may be necessary to demonstrate via headspace analysis that the packaging conditions provide an acceptable internal atmosphere or that the addition of some appropriate inert gas is necessary.[80]

The selection of the packaging components for liquid formulations is determined during preformulation development. The selection of a product package for liquids is linked intrinsically to the formulation and should be part of the multivariate analysis in the design of formulation development and optimization studies. The selection of rubber stoppers for parenteral liquids typically entails the examination of

extractables from the stopper in contact with the parenteral base formulation. Techniques for the selection of stoppers for parenteral powders include a dynamic headspace technique that models the absorption of rubber volatile components by the drug product.[81]

Microbiological Attributes

Microbial attributes are often thought to apply mainly to sterile drug products. However, a major focus of regulatory drug applications is the safety of the product. Associated with the safety of nonsterile products is the potential microbiological burden introduced by the raw materials and/or the processing environment. The Food and Drug Administration states in its microbiological inspection guide that each company is expected to develop microbial specifications for nonsterile products.[82] The Therapeutic Goods Administration, in promoting its stringent requirements for nonsterile pharmaceutical products, has published the results of its study on the microbial quality of nonsterile pharmaceuticals.[83] There is an attempt being made to harmonize proposed USP criteria for testing of nonsterile products with those proposed for the European Pharmacopoeia.[84] The microbiological burden for nonsterile products is particularly important for immunocompromised patients, and it has been argued that limits for oral products for this population must be tighter than those limits imposed on products with disease conditions not affecting immunity.[85]

The quality expectations for sterile products are clearly delineated in the United States and European Union (EU).[48,86] In addition, the product must meet compendial requirements (i.e., USP and European Pharmacopoeia). A strategy to control endotoxins in excipients also must be developed, with appropriate limits, dependent upon the route of administration and dosing regimen of the sterile product.[87]

Adequate process design and implementation of cGMPs provide assurance of acceptable bioburden or sterility because testing can identify only catastrophic failures. A review of the process design and the product flow should be performed to assure that appropriate techniques are used to produce drug products of acceptable microbial standards.

MANUFACTURER

The manufacturer and location of the drug product facility should be identified. An overview of the quality assurance aspects of the manufacturer may provide insight into the viability of the process. The due diligence reviewer should obtain a copy of the most recent cGMP manufacturing inspection issued by the FDA or the EU. The reviewer also should request copies of internal cGMP inspections. The regulatory and internal inspection reports provide a broad overview of the cGMP compliance aspects of the facility. Specific indications of issues concerning testing practices or other general cGMP compliance aspects will help to determine the reliability of the various data sets supplied by the manufacturer. If testing is performed at another facility, an investigation of the cGMP status of the testing facility is pursued.

An inventory of available drug products (suitable for clinical supplies) and critical components should be obtained. A review of supply agreements and contractual obligations for critical excipients should be reviewed to assure the availability of supplies. Alternate suppliers for critical materials should be identified.

Process Validation

Process validation is defined by the International Conference on Harmonisation (ICH) as the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a product meeting its predetermined specifications and quality attributes. The approaches to validation of a drug product are outlined in several regulatory guidance documents.[88,89] Some of the key aspects of validation are:

(1) Availability of a validation master plan or protocol with objectives, scope, and responsibilities outlined.
(2) Critical process parameters (key process variables) and their associated critical quality attributes identified.
(3) Key process data documented during validation.
(4) Acceptance criteria assigned for key process intermediates and final drug product.
(5) Three consecutive successful production batches produced.
(6) Reproducibility of the physicochemical profile of the drug product.
(7) Investigation of any atypical events or results occurring during validation runs.

Table 4 provides a checklist for due diligence drug product review of the manufacturing process development, the container closure system, the drug product microbiological attributes, and the manufacturer and process validation.

Description of Manufacturing Process and Process Controls

A flowchart summary of the process should be provided with the yields, operating conditions, and critical quality attributes for each intermediate indicated. The flowchart allows for an overview of the process and an outline for ease of discussion of the various steps.

A detailed narrative description of each step in the manufacturing process typically is available from early phase regulatory documents. This narrative should be compared with actual batch records from the manufacturing facility to make an assessment of the manufacturer's regulatory compliance. A detailed analysis of the manufacturing process should include a review of the quantities of excipients and reagents used, the identification of critical steps and process controls, the type and size of processing equipment used, and the operating conditions, such as temperature, pressure, pH, and mixing time. A review of the materials used in the manufacturing process should include availability and any safety concerns (the need for special processing equipment and protective gear for the operator). Some questions that should be asked include:

(1) What is the robustness of the process (are reworks common, and is the rework procedure well defined)? How do the physicochemical profiles of multiple lots compare? Are the characteristics of the reworked drug product consistent with historical data for the product?
(2) Have critical quality attributes for critical intermediates and final drug product been determined?
(3) Have critical processing parameters been clearly associated with critical quality attributes (are there data to support the association)?
(4) If the current process is labatory-scale or pilot-scale, can the batch size be increasedby using the current manufacturing technology (has a commercial manufacturing process been defined)?
(5) Is the batch yield acceptable relative to cost? This analysis will entail reviews with the business group to determine the acceptable cost of goods for the drug product.
(6) Are there any environmental or safety concerns?
(7) Is the current manufacturing process amenable to manufacturing capabilities at existing plants? Are the technologies used in the process common; is special equipment required?
(8) Is the cycle time for processing of the drug product acceptable?

Table 4. A summary checklist of key CMC review aspects of drug product—manufacturing process development, container closure system, drug product microbiological attributes, manufacturer and process validation.

Manufacturing process development
Defined quality attributes
Process development changes
Process/clinical studies correlation
Critical process parameters
Critical quality attributes
Multivariate analysis
Historical batch data
Rework
Filter compatibility for liquids
Cleaning validation
Container closure system
Functional requirements
Critical component parameters
Compatibility testing
Drug product microbiological attributes
Nonsterile products
Sterile products
cGMP controls
Process design implications
Compendial requirements
Endotoxin control
Manufacturer
Location
Manufacturing facility cGMP status
Testing facility cGMP status
Inventory of drug product and key ingredients
Contractual obligations
Alternate suppliers of critical materials
Process validation
Process validation data available
Validation master plan or protocol
CPPs and their associated CQAs identified
Documentation of key process data during validation
Acceptance criteria for key process intermediates and final drug product
Three consecutive successful production batches
Reproducibility of the impurity profile

(9) Have suitable process hold points been determined? What is the impact of holding intermediates on the quality/stability of drug product? Have bulk hold studies of intermediates been performed?
(10) Are any of the excipients of animal origin? If so, is their transmissible spongiform encephalopathy (TSE) status documented?[90]
(11) Are any of the manufacturing steps patent protected?

Control of Excipients

The acceptance criteria and tests conducted for the excipients should be reviewed relative to the preformulation experimental results. The acceptance criteria for the excipients should consider those qualities critical to the drug product performance and manufacturing operation as described earlier in formulation development.

Description of Analytical Methods

The analytical methods used to test excipients, reagents, and drug product should be reviewed. Sufficient detail should be available in order that the methods could be adequately run in the laboratory. For example, HPLC methods should provide detail on the type of column used, run time, mobile phase composition, flow rate, and detection means. Adequate validation data should be available to assure the accuracy of the data used to support the physicochemical properties of the drug product. The ICH text on the validation of analytical procedures provides a good overview of the type of information that should be included in the validation package.[91] Key items include accuracy, linearity, precision (repeatability and intermediate precision), robustness, and specificity. While all of these aspects of validation may not be complete in early phases of development, some level of detail must be available to assure the accuracy of the information provided.

CONTROL OF DRUG PRODUCT

Specifications

Specifications consist of test methods and their associated acceptance criteria. Each specification should be presented with a rationale for the limits specified. The following tests and acceptance criteria are applicable to all drug products[92]:

(a) Description—a qualitative statement regarding the appearance of the drug product is given. The drug product acceptance criteria entails the observed drug product meeting the given qualitative criteria.
(b) Identification testing should distinguish between the drug substance in the drug product and closely related compounds. Typically, two identification tests are performed with one test being the HPLC retention time match with a reference standard material. The second test typically is a spectroscopic technique such as IR. It should be noted that ultraviolet-visible absorbance spectra generally are not specific enough to distinguish related compounds.
(c) Assay—The most common assay procedures for drug products are titration methods and HPLC methods. If a titration method is used for assay, an additional specific, stability-indicating method should be used to control impurities in the drug product.
(d) Impurities—HPLC methods commonly are used to control impurities in drug product. The methods should be specific and stability-indicating.

There are additional specifications that may be applicable, depending upon the nature of the drug product. These specifications include:

(1) Disintegration.
(2) Dissolution.
(3) Stereoisomeric purity.
(4) Moisture (water).
(5) Residual solvents.
(6) Microbial limits.

For drug product suspensions and solutions, additional physicochemical characteristics of the drug product may impact the drug product performance. These characteristics include:

(1) pH of solution.
(2) Particle size of suspended drug.
(3) Clarity of solution (turbidity).
(4) Color of solution.
(5) Viscosity.

(6) Volume of fill.
(7) Preservative testing.

Table 5 provides a checklist for due diligence drug product review of the description of the manufacturing process and process controls; control of excipients and control of the drug product.

Analytical Procedures and Validation

As detailed previously for the control of excipients, reagents, and drug products, sufficient detail should be provided in order that the methods could be adequately run in the laboratory. Control methods derived from compendial references should detail any requisite sample preparation requirements and any other details, such as the column used in the HPLC method. A review of the method validation package should ensure that all ICH guidelines are met.

Batch Analyses

Test results for all batches made (including small-scale batches) should be reviewed. A comparison of results for those batches used in phase I safety studies with those batches made for later clinical studies should be pursued. The level and type of impurities in the later-phase clinical batches should not exceed that of the phase I safety batches.

Justification of Specifications

Drug product specifications should provide comprehensive control of identity, purity, quality, and potency. The specifications for the drug product should be consistent with current process capability and drug safety study results. During early stages of development, justification of specifications is not available because final specifications are determined by the comprehensive development experience. If the drug product is in phase III of development, draft final specifications should be justified with regard to the historical experience with the process at the current scale and manufacturing process. At phase III, the drug product process should be well defined and not open to any significant changes since phase III stability batches and pivotal clinical studies will use drug product from the current process.

Table 5. A summary checklist of key CMC review aspects of drug product—description of the manufacturing process and process controls; control of excipients and control of drug product.

Description of manufacturing process and process controls
Process flow diagram
Batch records
Critical quality attributes
Scale-up
Process controls
Safety
Key starting materials
Operating conditions
Batch size
Batch records
Scale-up (commercial process defined)
Process capable of being run in existing plants
Cycle time
Process hold points identified
Reagents of animal origin and TSE status
Safety
Environmental issues
Robustness of process and rework frequency
Ingredient availability and cost
Patent protected process steps
Special equipment required
Control of excipients
Test methods
Acceptance criteria
ICH criteria for validation
Control of drug product
Description
Identification testing
Assay
Impurities
Disintegration
Dissolution
Stereoisomeric purity
Residual solvents/moisture
Specifications justified
Specifications consistent with process data

REFERENCE STANDARDS OR MATERIALS

The validity of the analytical results provided is, in part, reliant upon the use of appropriate reference standards. Reference standards used in the analysis of drug product, starting materials, and intermediates must have additional testing to verify the identity and purity of the reference standard. Typically, the reference standard is fully characterized, including structural elucidation data, as well as extended testing for impurities. Once the reference standard is fully

characterized, a secondary reference standard may be tested against the primary standard and used for routine testing.

CONTAINER CLOSURE SYSTEM (PACKAGING MATERIAL)

Primary Packaging

A full description of the primary package of the drug product should be given. The potential for any incompatibility of the package and the drug product should be discussed.

The chemical and physical reactivity of the drug product will dictate the type of packaging needed. For example, a hygroscopic drug product may require the inclusion of desiccants in the package container. For a drug product sensitive to environmental conditions (e.g., heat, light, moisture), data on the qualification of the packaging component should be given. Once the critical package parameters are identified, these parameters should be tested routinely on the incoming containers. A minimum of identification testing should be performed for the packaging material regardless of the functionality of the packaging component. Techniques such as FTIR identity for polyvinyl chloride films commonly is applied.[93]

Secondary Packaging

Any secondary package used for the drug product should be described (e.g., cardboard box). If the secondary packaging material provides protection to the product, test results of stability studies with and without the secondary package should demonstrate the adequacy of the secondary package.

STABILITY

Batches Tested

A review of all stability batches is performed. Special attention should be given to any increase in impurities or appearance of a new degradation product. The amount of variability seen between batches in the level of degradation products may be indicative of the robustness of the drug product manufacturing process. The appearance of new impurities or changes in impurity levels are consistent with poorly controlled processes. The degradation pathway for the drug product and any critical intermediate should be elucidated.

Summary of Forced Degradation Studies and Stability Studies Under Stress Conditions

Forced degradation studies are performed as part of the drug product method development. The treatment of the drug product with light, heat, moisture, acid/base, and peroxide provides a means to demonstrate that the analytical method to control the drug substance assay/impurity is indeed specific

Table 6. A summary checklist of key CMC review aspects of drug product—control of drug product (suspensions and solutions), analytical methods, batch analysis, container closure system and stability.

Control of drug product (suspensions and solutions)
pH of solution
Microbial limits
Particle size of suspended drug
Clarity of solution (turbidity)
Color of solution
Viscosity
Volume of fill
Preservative testing
Specifications justified
Specifications consistent with process data
Analytical methods
Review of analytical methods—details adequate
Validated methods
Methods provide sufficient specificity
Accuracy
Linearity
Precision
Robustness
Control of potential impurities
Batch analyses
Test results for all batches made (including small scale batches) should be reviewed
Container closure system (packaging material)
Primary package compatibility
Qualification
Critical package parameters
Stability
A review of all stability batches
Impurity profile
Forced degradation studies
Degradation pathway elucidated

and stability-indicating. The data produced in accelerated studies also provides information to the due diligence reviewer regarding potential processing issues (e.g., light protection) that might be necessary in the manufacture of the drug product. Ideally, some level of degradation should be produced (~5–10%) during the forced degradation studies to demonstrate the specificity of the method and to provide information on the degradation pathways of the drug product. Therefore, depending upon the intrinsic stability of the product, it may be necessary to adjust the relative intensity of the degradation conditions.

Table 6 provides a checklist for due diligence drug product review of the control of the drug product (suspensions and solutions), analytical methods, batch analysis, container closure system, and stability.

CONCLUSION

Pharmaceutical drug product due diligence is a detailed investigation of the chemistry, manufacturing, and controls (CMC) information associated with a drug product and serves to assure that an adequate level of quality exists for the given compound to allow for successful commercialization of the drug. A scientific review of the pertinent development data provides the necessary information to assure that informed decisions are made regarding the potential in-licensing of a development compound.

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