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⟨1149⟩ GUIDELINES FOR ASSESSING AND CONTROLLING THE PHYSICAL STABILITY OF CHEMICAL AND BIOLOGICAL PHARMACEUTICAL RAW MATERIALS, INTERMEDIATES, AND DOSAGE FORMS

INTRODUCTION

The physical stability of pharmaceutical materials (e.g., excipients, active ingredients, intermediates) and drug products is an important property to consider when developing any new medicine, as the following considerations illustrate:

- Physical changes have been the cause of some high-profile product recalls and reductions in product shelf-life (*1*). Recalls have occurred for a drug product from the US marketplace due to changes in the unexpected appearance of a more stable and less soluble crystal form and for a transdermal system after crystals formed unexpectedly and compromised its efficacy.
- As recently as the 1980s, the screening of drug substances for polymorphism and for the ability to form salts/co-crystals and hydrates/solvates ("pseudopolymorphs") was not routine at many companies. Hence, there was limited awareness of the risks of physical transformations occurring during the manufacture, storage, and use of pharmaceutical dosage forms (*2*).
- Since the 2000s, there has been a marked increase in the use of amorphous drug substances and intermediates, increasing the probability of physical instability occurring because of recrystallization (*3*).
- There has been an increased understanding of the risks of developing salt forms of weak bases, which can disproportionate in the presence of excipients commonly used to manufacture immediate-release solid oral dosage forms (*4*).

This general information chapter is focused on changes in those physical attributes that can directly affect the safety, quality, and efficacy of pharmaceutical materials, systems, or products. Further, the scope of this chapter is intended to cover all materials and dosage forms described in the *USP–NF*, including drug substances, drug product intermediates, excipients, solid/liquid/semi-solid dosage forms, sterile and nonsterile preparations, and diagnostic materials.

Even small changes in the critical physical attributes of an excipient, drug substance, intermediate, or drug product over time can affect the shelf life of a material and any product manufactured from it. Several health authorities have discussed this topic in guidance documents and articles (see *Appendix 1*). In addition, several national pharmacopeias have mentioned physical stability testing and control topics in their monographs and chapters.

Clearly, certain health authorities and official compendia consider physical properties to be potentially critical quality attributes (CQAs) for excipients, drug substances, drug products, and related materials (e.g., intermediates) for some dosage forms. As a result, demonstration of 1) manufacturing processes capable of producing drug substances and drug products of consistent physical quality at release and 2) the physical stability of those materials during storage is required for successful regulatory filing and approval of marketing applications (e.g., new drug applications and marketing authorization applications).

DEFINITION OF PHYSICAL STABILITY

Physical stability is the ability of a material to remain physically unchanged over time under stated or reasonably expected conditions for manufacturing, storage, and use. However, while this simple definition is quite useful, it does not cleanly distinguish between a purely physical change and a purely chemical change. For instance, if the color of a solution (a physical property) changes, this could be due either to a change in the ionization state of the compound containing the chromophore (a physical change) or to a change in the chemical structure of the compound containing the chromophore (a chemical change). Furthermore, ultraviolet-visible spectrophotometry (a physical test method) could be used to characterize either the change in ionization state or the change in chemical composition. Additionally, sometimes degradation pathways are synergistic: a chemical degradation event triggering a physical event, such as when oxidation is followed by aggregation in a protein biologic. Thus, while this chapter focuses on instabilities that arise from physical causes, its discussion unavoidably overlaps (in terms of cause, observation, and consequence) with instabilities arising from chemical changes.

According to fundamental physics, physical instability is often the result of the physical forces of interaction. The commonly accepted physical forces of interaction are van der Waals forces (such as the London dispersion force, Debye force, and Keesom force); hydrogen bonding; and electrostatic interactions. Hydrogen bonding is separate from the Keesom force because a hydrogen bond has too much electrostatic character to be considered a true Keesom force. An important characteristic of all of these forces is that they are reversible. In other words, a physical bond or interaction can be readily reversed to restore the original species, in contrast to covalent bond formation,

wherein the original reactants cannot be easily restored. Thus, the physical forces of interaction are fundamentally different in both mechanism and consequence from the formation of a chemical (or covalent) bond.

Temperature, pH, light, pressure (including water vapor pressure), gravity, and shear force may all influence the aforementioned physical forces. They may also influence the interfaces across which the physical forces of interaction may be operating or the bulk phase through which those physical forces of interaction may be operating. The interplay among temperature, pressure, gravity, and the physical forces of interaction can lead to some seemingly inconsistent observations. For example, someone who has tried to resuspend a non-flocculated caked suspension will likely find it hard to accept the fact that physical interactions are reversible. In that case, the settling that occurred under the influence of gravity created significant areas of true contact between the particle surfaces. Those areas of true contact lead to an increased number of interparticulate interactions. Weak interactions, when present in great number, can be significant. However, in spite of that strength, the input of a sufficient amount of energy will regenerate the original particles. An exception to this example would be when the particles have been settled for sufficiently long periods of time and drug dissolution or precipitation have further strengthened the cake. Dissolution and precipitation are reversible processes. However, as a result of these processes, the original particles cannot be regenerated because they no longer exist. Interestingly, all of the individual processes resulting in such cake formation are reversible, but, in total, they may lead to an irreversible change in the system.

There also may be cases for which the system is reversible, but the packaging makes it functionally irreversible. An example would be the phase separation of an ointment. If the phase-separated ointment has not been packaged, it could be presumably returned to its original state by high-shear mixing. However, such mixing is not possible when the separation occurs after packaging (assuming that the ointment was packaged in a collapsible tube). Thus, the packaged product may have undergone an irreversible physical change.

In conclusion, when considering the physical stability of pharmaceutical materials and products, one should think carefully about the underlying mechanism involved and not solely consider the measurement technique or observation.

COMMON TYPES OF PHYSICAL INSTABILITY

Several common types of physical instability may occur for excipients, drug substances, drug product intermediates, and drug products (see *Table 1*, *Table 2*, *Table 3*, *Table 4*, *Table 5*, and *Table 6*). Such instabilities can occur during storage of the raw materials, during manufacture of the drug product, or during the storage, distribution, and use of the drug product. With the proper controls in place, these potential instabilities can be often minimized or avoided. However, without such precautions, the integrity of the product can be seriously compromised.

The common instabilities or "failure modes" can be classified as "critical," "major," or "minor" depending on the defect's impact on patient safety or product efficacy. Critical failure modes are known to affect patient safety or product efficacy, whereas a major failure mode is likely to affect safety or efficacy. Finally, minor failure modes do not affect patient safety or product efficacy.

A major challenge when classifying any given failure mode is that the classification of a failure mode is often highly dependent on the type of product being considered. For example:

- For small molecule drug substances, if the crystal form of an oral Biopharmaceutics Classification System (BCS) Class I drug (i.e., drug with high solubility and high permeability) changes and the new crystal form still meets the solubility requirements for a BCS Class I drug, the failure mode could be considered minor. However, if the solubility of the new crystal form becomes substantially lower than the original crystal form, the failure mode is likely major or critical because the physical instability leads to a change in the dissolution rate of the drug product.
- For biologic substances and products (as opposed to small molecule pharmaceutical products), there are different types of physical instability, and thus different failure modes and risk factors. The unique structures of protein biologics are critical for their precise biochemical function; therefore, physical stability is dependent on the proper folding of their native state and appropriate structural maintenance. Aggregation is a primary mode of physical instability. Aggregation can occur in solution or on surfaces due to absorption, and it can be either reversible or essentially irreversible. Such changes can lead to a loss of activity as well as other critical problems, such as toxicity and immunogenicity.

Table 1. Examples of Physical Instability Leading to Changes in Appearance

Material	Failure Mode	Example Cause(s)
Powders (such as excipients and drug substances)	Caking or agglomeration/aggregation	Temperature cycling during storage and distribution, water sorption, and presence of electrostatic charge
	Appearance change upon storage	Change of crystallinity, polymorph change, change in hydration state
Tablets	Appearance change upon storage	Spontaneous salt formation between a drug substance and an excipient
	Breakage or chipping	Water sorption or loss by an excipient
Solution	Appearance change upon storage	Chemical reaction or degradation

Material	Failure Mode	Example Cause(s)
	Particulate formation	Insoluble salt formation between drug substance and preservative
	Haze formation/opalescence, which can lead to subvisible or visible particulate	Chemical degradation leading to the formation of an insoluble product, microbial growth, or product–package interaction
	Fibril or particulate formation	Aggregation (biologics) due to stressors such as shear forces
	Gelling	Protein unfolding, hydrogen bonding, liquid crystal formation, intermolecular interactions
Powder (prepared as a lyophilized cake)	Collapse of lyophilized cake	Crystallization of excipient or drug substance; storage temperature greater than glass transition temperature
	Increased reconstitution time	Crystallization of excipient or drug substance; storage temperature greater than glass transition temperature
Emulsion	Appearance change	Droplet coalescence over time
	Phase separation	"Cracking" of emulsion due to temperature cycling upon storage
Gel	Appearance change	Dehydration of gel due to inappropriate storage conditions
	Inhomogeneous polymer cross-linking of the gel or a change in composition of the liquid	Weakness of gel structure

Table 2. Examples of Physical Instability Leading to Changes in Dissolution and Disintegration

Material	Failure Mode	Example Cause(s)
Excipient	Failure (for a super-disintegrant) to promote disintegration	Prior water sorption under high humidity storage conditions
Drug substance	Slowed dissolution rate	Particle agglomeration upon storage due to surface disorder induced by milling; crystallization of amorphous drug; polymorphic transitions
Tablets/capsules	Change in dissolution rate	• Crystal form change • Crystallization of amorphous drug • Water migration within dosage form • Disproportionation of drug substance salt • Cross-linking of gelatin capsule
	Change in disintegration time	• Water migration within dosage form • Cross-linking of gelatin capsule
Suspension	Change in dissolution (of the suspended particles) rate	Increase in particle size, agglomeration

Table 3. Examples of Physical Instability Leading to Changes in Tablet or Capsule Mechanical Properties

Material	Failure Mode	Example Cause(s)
Excipient	Loss of tabletability	Water sorption from environment, polymorph change
Drug substance	Loss of tabletability	Particle agglomeration upon storage due to surface disorder induced by milling
Tablets	Change in breaking force	• Crystal form change • Water sorption or desorption • Water migration within dosage form
	Change in disintegration time	• Water uptake • Water migration within dosage form
Capsules (hard or soft shell)	Loss of mechanical strength or integrity	• Water sorption by gelatin capsule • Water redistribution within dosage form • Inadequate primary packaging

Table 4. Examples of Physical Instability Leading to Changes in Rheological Properties of Suspensions or Solutions

Material	Failure Mode	Example Cause(s)
Suspension	Change in viscosity leading to dosage non-uniformity via sedimentation	Molecular weight change of suspending agent caused by increased temperature
		Increase in suspended particle size/change in morphology (e.g., Ostwald ripening)
Solution	Change in viscosity, precipitation of the solute	Molecular weight reduction of the solvent caused by increased temperature
		• Increase in solute size/change in morphology (e.g., Ostwald ripening) • Changes in solubility with temperature

Table 5. Examples of Physical Instability Leading to Changes in Rheological Properties of Semi-Solid Products

Material	Failure Mode	Example Cause(s)
Excipient	Change in viscosity	Molecular weight reduction caused by high-shear
Emulsion	Change in viscosity	Increase in globule size upon temperature cycling
Gel	Change in yield stress	Phase separation ("syneresis") caused by temperature cycling or other improper storage conditions
Ointment	Change in viscosity	Drug substance recrystallization

Table 6. Examples of Physical Instability Leading to Changes in Performance of Inhaled and Nasal Drug Products

Material	Failure Mode	Example Cause(s)
Dry powder inhaler (drug product)	Variable dose delivery due to change in aerodynamic particle size distribution (APSD)	Change in interparticulate interactions due to uncontrolled storage humidity and temperature (e.g., capillary forces progress into solid bridges)
		Crystallization of amorphous material (excipient and/or drug substance)
Metered dose inhaler (particles in liquid suspension, drug product)	Variable dose delivery	Agglomeration and then aggregation of drug substance primary particles due to temperature excursions during storage
Nasal spray (drug product)	Subpotent dose delivered	Precipitation of less soluble drug substance polymorph or solvate/hydrate
		Precipitation of insoluble complex between drug substance and excipient

COMMON RISK FACTORS

Based on the observations of common physical instabilities (see *Common Types of Physical Instability*) a number of common risk factors can be identified. Examples are listed below.

For excipients and drug substances:

- Materials with a low melting point (typically less than 100°) may have a greater tendency to undergo phase changes during manufacturing, distribution, storage, or use
- Acids and bases will have a tendency to form salts when mixed together
- Hygroscopic materials will tend to absorb water from their surroundings, and this may accelerate moisture-mediated physical changes (such as the softening of tablets or the crystallization of amorphous components)
- Materials with a tendency to form hydrogen bonds may be susceptible to forming hydrates or co-crystals when mixed with polar materials
- Amphiphilic materials may form liquid crystalline phases and undergo gelling

For drug substance and drug product manufacturing processes:

- High-shear processes (such as milling, homogenization, or stirring) can induce physical changes in common pharmaceutical materials
- Processes that involve heating and cooling can trigger unwanted phase changes
- Processes utilizing solvents (including water) also can be risk factors for physical instabilities due to the possibility of dissolution and precipitation
- Changes in pH or ionic strength may induce aggregation of proteins and peptides, sometimes synergistically with specific processing conditions (such as high shear forces, changes in hydrophobic surface interactions)
- Terminal sterilization processes may induce physical changes (for example, processes involving high heat sterilization may affect viscosity and particle size distribution and osmolality of a suspension; high temperature and changes in hydrophobic surface interactions may induce aggregation/fibrillation of proteins and peptides)

For the storage and distribution of raw materials, intermediates, and drug products:

- Poorly controlled temperature and humidity conditions can trigger physical instabilities for many materials
- Primary packaging that does not provide adequate protection from environmental conditions (such as humidity) can be a risk factor for physical instability
- Physical changes often can be triggered by in-use conditions that expose the product to elevated temperature or humidity or excessive agitation

All of these material and process risk factors should be considered carefully during the design of the formulation (including excipient choice) and the selection of the manufacturing process and the packaging system. These risk factors may not be important for all types of dosage forms (e.g., simple solutions), but they need to be determined for each individual situation. Consideration of the various risk factors should also occur when deciding upon the best control strategy to ensure product quality and when determining whether or not detailed physical testing is needed during product development.

ANALYTICAL TESTING CHALLENGES

Historically, the detection and quantitation of physical changes in a drug substance, excipient, drug product intermediate, or final dosage form have created significant analytical challenges. Only in recent years has instrumentation, with the necessary selectivity and sensitivity,

become commonly available so that significant numbers of samples (needed for meaningful trend analysis) can be quickly and reproducibly tested.

Usually, the physical properties of greatest interest will be those related directly to product performance or CQAs. These properties may be directly or indirectly dependent on the physical stability of individual components or on the product as a whole. Such properties may be investigated as part of the pharmaceutical development process, may be monitored during manufacturing or at the time of product release, or may be tested throughout long-term stability studies.

Common analytical testing challenges include the following:

- Physical stability testing methods (see *Appendix 2*) may require specialized instrumentation and expertise. Examples include optical microscopy, scanning electron microscopy with energy dispersive spectroscopy (SEM/EDS), moisture sorption, laser diffraction (Mie or Fraunhoffer), thermal analyses, Fourier-transform infrared spectroscopy (FTIR), Raman spectroscopy, near-infrared (NIR) spectroscopy, rheology, mercury porosimetry, X-ray diffraction, and solid-state nuclear magnetic resonance (solid-state NMR). Additional techniques used for biologics include circular dichroism, size-based analysis (analytical ultracentrifuge, light scattering, size-exclusion chromatography), and techniques to study the three-dimensional structure such as hydrogen/deuterium exchange mass spectrometry, X-ray crystallography, and electron paramagnetic spin resonance spectroscopy. Some of these methods are more complex than other orthogonal techniques, and therefore are suitable for the product development phase and not for routine testing of commercial products. For example, solid-state NMR may be used as a development tool, but Raman spectroscopy may suffice for physical form monitoring of a commercial product. Similarly, a rheometer may be needed to fully characterize a liquid, ointment, or cream, but a viscometer may suffice to show the consistency of well-characterized commercial drug product.
- Physical test methods often require slow and very labor-intensive sample preparation that does not perturb the physical properties of the samples. Ideally, whole dosage forms should be analyzed without the need for pulverization, sub-sampling, dilution, or other alterations.
- The limits of detection for physical changes often can be much higher than for chemical test methods. For example, detecting a physical polymorphic change of less than 5% (by volume or mass/weight) is quite difficult in most cases and often requires exquisite control of the sample preparation as well as the test methodology. Likewise, viscosity changes (e.g., in semi-solids) are frequently logarithmic in nature, and in this situation 5% to 10% variability would be quite normal.
- Among the most important properties to understand for solid dosage forms is the moisture sorption behavior of the individual components. Water is one of the most influential factors affecting the physical stability of solids. Understanding the moisture content and how it may change during the testing process is also critical.
- Single-component materials represent a limiting case of "product". These generally include the drug substances, excipients, specific phase impurities, and perhaps packaging components (e.g., a desiccant). Formulated products present additional challenges, not only due to matrix effects but also for appropriate sample preparation.
- Quantitative measures are desired where possible. This depends first on the inherent characteristics of the technique; some are inherently qualitative or non-specific.
- Another challenge may be the availability of suitable, stable reference materials and the ability to present them in a context that is equivalent to the analyte. Spiking known amounts of a drug substance into a placebo formulation is one common approach, but accurate results only can be obtained with proper sample preparation, especially for low concentrations and/or low drug loads in solids, semi-solids, and high-viscous liquids.
- For best quantitation, an analyte must be stable during sample preparation and analysis. Ideally, each analyte would be prepared in an identically processed matrix; however, this is rarely possible. The best practice is to keep the matrices as similar as possible.
- It may be necessary to build empirical models to describe the concentration-response relationship using reference standards to estimate the amount of physical change that has occurred. Such models may not transfer well from instrument to instrument, or they may "drift" over time because of changes in instrument sensitivity.
- Standard chemical stability approaches may not work when applied to physical stability studies. For example, applying the Arrhenius extrapolation could be misleading because physical changes can occur abruptly with a shift in temperature. Additionally, elevated temperatures (e.g., 40°) may be above a phase transition point (e.g., the melting point of a semi-solid). Therefore the "accelerated" conditions commonly used for chemical stability tests may prove to be meaningless for physical stability studies.

As mentioned above, there often will be a need for enhancing the sensitivity of physical stability-indicating methods, for several reasons. In managing the product matrix effects, two factors should be considered: dilution and interference. For a single component in a drug product (such as the drug substance), detection and quantitation limits may be affected simply by the lower concentration of the component in the product matrix (e.g., for a product with a 10% drug load, a 5% detection limit for a phase impurity in a drug substance could result in an effective detection limit of only 50%). Product components other than the analyte could also give responses. If such responses overlap with those of the analyte, the sensitivity of the method would be diminished or the method could become unsuitable. Especially for early studies, improved sensitivity could allow for more accurate prediction of the expected shelf-life using shorter time frames. Common approaches for increasing sensitivity and managing matrix effects include: 1) using longer data collection times to provide better signal-to-noise ratios, 2) changing or limiting the spectral or scan range to avoid interferences, and 3) adjusting the concentration or separation of the analyte.

Some analytical challenges may require the use of orthogonal techniques to provide desired information; for example, where interferences or other matrix effects preclude the use of a desired technique. Even if qualitative, such methods could still be useful. Additionally, the use of multiple techniques may be required to profile the physical stability characteristics of the molecule or product to maximize the potential to

detect issues or differences (useful in biological comparability exercises). These considerations may be important in the development of product understanding and ultimately an appropriate control strategy, as discussed in the next section.

BUILDING AN APPROPRIATE CONTROL STRATEGY

A risk-based scientific approach is recommended to ensure product quality throughout development and commercialization. An enhanced product development approach, such as Quality-by-Design (QbD), should be applied to ensure a systematic evaluation and understanding of the critical physical attributes of materials/products and of functional relationships that link the material/product physical attributes and process parameters to product CQAs.

Attributes of QbD include:

- Identifying all possible influences that may affect product performance
- Using risk assessment, guided by scientific knowledge and experience to identify potentially high-risk attributes or parameters
- Designing and executing experiments to determine whether the influence should be considered critical and at what levels (as such, edge of failure experiments at early development stages are encouraged)
- Developing a control strategy that focuses on defining acceptable ranges for the critical attributes/parameters
- Submission strategy and impact classification are determined by the innovator based upon regulatory expectations and sound scientific strategy, which may include design space experimentation but may not meet the expectations of a QbD submission

Perhaps the most important aspect of developing a physical stability control strategy is understanding the underlying mechanisms of physical instability. This usually requires understanding the properties and variability of individual components as well as the product as a whole. Some CQAs may be indirectly related to the causative physical changes. For example, the dissolution behavior of an oral dosage form could be affected by multiple underlying physical changes, such as changes in tablet breaking force or interactions between the drug substance and excipients, or drug substance polymorphic change.

The potential physical instability of a product should be considered throughout the product development process. Ideally, it should be addressed as early as the point at which the drug substance form is selected. If solubility, purity, crystallinity, and mechanical properties are not limiting the manufacture and bioavailability of a drug substance, the solid form that exhibits better physical stability should be selected. For example, the polymorph of a drug that is thermodynamically stable at ambient conditions is usually chosen to minimize the chance that a physical form change could occur during normal storage and use.

Formulation design and packaging selection may be used to build physical stability into the product. For biological pharmaceuticals, the formulation design may include choosing such excipients as buffers, amino acids, polyols/disaccharides/polysaccharides, or surfactants, to optimize physical stability (e.g., at a specific pH) or protect the protein. Platform formulations may be used early in development, followed by further characterization and screening of excipients/ranges to define the optimum combination to ensure physical stability throughout shelf-life. Reformulation may be required to maintain physical stability as target product profile changes occur during development or product life-cycle changes occur (e.g., moving to a subcutaneous formulation at a higher protein concentration).

The International Council for Harmonisation [ICH Q8(R2)] recommends drug-excipient compatibility studies to facilitate the early detection of, and understanding of, physical and chemical incompatibilities (5). Compatibility studies can enhance the understanding of drug-excipient interactions and can help with root cause analysis if stability problems occur.

In some cases, excipient hygroscopicity may facilitate phase changes such as disproportionation of a salt, hydration of an anhydrous drug, or crystallization of an amorphous form. Thus, if possible, hygroscopic excipients should be avoided. When hygroscopic excipients must be used for certain functionalities, appropriate strategies to control exposure to high humidity should be implemented.

Some excipients may react with drug substances to form a new solid phase, such as a salt or co-crystal. Ion exchange between some drugs and excipients may lead to changes in the dissolution rate of tablets. A drug substance may also form a less-soluble complex with an excipient and thus could precipitate out from a solution formulation.

Major changes in physical properties are often mediated by exposure to high temperature or humidity. To avoid unintended physical instability of a drug product, it is important to understand the temperature and humidity sensitivity of the components in the product. For example, an anhydrous drug or an excipient may undergo hydration when exposed to high relative humidity (RH). In that case, high RH conditions should be avoided during distribution, storage, and use.

When problems are recognized but a simple solution is not readily available, the formulation design, critical manufacturing process parameters, in-process controls, packaging selection, and controlled storage conditions should be used to minimize physical instability and help ensure adequate shelf-life of the drug product. The selection of protective packaging must align with the purpose of stabilizing the drug product. In cases where moisture-induced phase changes in a drug product are problematic, moisture-resistant packaging may be used to maintain physical stability of the drug product after it has been dispensed to patients. Blister packing of individual tablets is one example. Adding moisture-absorbing desiccant packs to a bottle is another example. Sometimes, tablets do not have sufficient strength to withstand stress during handling. For example, use of rayon/polyester coil or the use of a desiccant sachet instead of a desiccant canister should be considered to avoid excessive agitation/stress. In those cases, the package should provide protection against excessive stresses during storage and handling. If the drug product's sensitivity to temperature is confirmed, high-temperature situations should be avoided during transportation and use of the product by patients. In extreme cases, refrigerated storage may be required.

For products that do have potential physical instability problems, a modified testing plan may be required. For example, it may be necessary to demonstrate using additional studies that the physical changes do not have any impact on the bioperformance of the product.

Alternatively, a limit test may need to be developed to determine the extent of physical change that occurs over the shelf-life of the product or during normal use by patients. Additional tests also may be needed when a product has arrived at its intended destination, or even before

it is dispensed to patients.

Finally, where a test method is implemented to assess the extent of a physical change in a raw material or dosage form, it is then necessary to ask how much change is acceptable. There is no universal answer to this question, and each case must be considered on its own merits. A color change that only occurs once the primary package is opened and has no impact on product performance or patient safety may have quite wide limits of acceptability, whereas a drug substance phase change that slows the dissolution rate of a solid dosage form may require quite stringent limits set over the entire lifetime of the product. To ensure that an appropriate control strategy is in place, extensive testing may be needed during product development. Such testing may then alleviate the need for validated methods for those products when manufactured commercially, either by showing that under standard conditions adverse physical changes do not occur, or that such occurrences may be alleviated by use of proper packaging.

In general, validated physical test methods are less prevalent than validated chemical test methods. The development of a validated solid-state analytical method may be required in some instances. In other cases, less complex approaches may be preferred provided they are supported by earlier research during the development phase of the product. See *Validation of Compendial Procedures* ⟨1225⟩ for more information on the validation of physical methods.

CONCLUSION

Physical instability of pharmaceutical materials, including active ingredients, excipients, drug product intermediates, and finished drug products, is a well-recognized phenomenon that is documented in the literature. Regulatory agencies around the world have provided guidance that highlight the importance of physical stability in pharmaceutical development and its role in the stability of drug products over their shelf-life. Physical instability can affect the quality, safety, and efficacy (bioperformance) of the drug product and its subsequent life-cycle. Irrespective of the level of changes in product quality or performance, a systematic investigation and selection of suitable forms of drug substance and formulation ingredients are recommended early in the drug development process to create a mechanistic understanding of the process involved in the instability. Particularly pivotal for the enhancement of this understanding will be the judicious selection of a sensitive analytical technique and the optimization of the data acquisition process.

The overarching understanding, such as that may be gained through a QbD approach, will assist in identifying risks and vulnerabilities associated with drug product manufacturing, storage, and use, which will ultimately facilitate implementation of a control strategy. The understanding will also contribute to informed decisions regarding the selection of storage conditions and appropriate packaging materials, as well as the possible need for validated test methods.

APPENDIX 1

Examples of Guidelines and Guidances Used by Health Authorities That Mention Physical Stability

Health Authority	Guideline or Guidance
International Council for Harmonisation (ICH)	Q1A: Stability Testing of New Drug Substances and Products (6) Q1B: Stability Testing: Photostability Testing of New Drug Substances and Products (7) Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (8) Q8 (R2): Pharmaceutical Development (5) Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) (9)
US Food and Drug Administration (FDA)	Drug Stability Guidelines (10) (for animal drugs) Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products—Quality Considerations (11) Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products—Chemistry, Manufacturing, and Controls Documentation (12) Liposome Drug Products—Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation (13) ANDAs:[a] Stability Testing of Drug Substances and Products (14) ANDAs: Stability Testing of Drug Substances and Products—Questions and Answers (15) ANDAs: Pharmaceutical Solid Polymorphism—Chemistry, Manufacturing, and Controls Information (16)
European Medicines Agency (EMA)	Note for Guidance on In-Use Stability Testing of Human Medicinal Products (17) Guideline on Stability Testing for Applications for Variations to a

Health Authority	Guideline or Guidance
	Marketing Authorization (18) Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products (19) Reflection Paper on the Data Requirements for Intravenous Liposomal Products Developed with Reference to an Innovator Liposomal Product (20)
World Health Organization (WHO)	Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products (21)

[a] Abbreviated new drug applications.

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APPENDIX 2

Examples of Physical Test Methods and Information in the *USP–NF*

General Chapters
Spectroscopic Identification Tests ⟨197⟩
Light Diffraction Measurement of Particle Size ⟨429⟩
Visual Comparison ⟨630⟩
Color and Achromicity ⟨631⟩
Completeness of Solution ⟨641⟩
Globule Size Distribution in Lipid Injectable Emulsions ⟨729⟩
Dissolution ⟨711⟩
Optical Microscopy ⟨776⟩
Optical Rotation ⟨781⟩
Osmolality and Osmolarity ⟨785⟩
Particle Size Distribution Estimation by Analytical Sieving ⟨786⟩
Subvisible Particulate Matter in Therapeutic Protein Injections ⟨787⟩
Particulate Matter in Injections ⟨788⟩
▲*Subvisible Particulate Matter in Intraocular Solutions* ⟨789⟩▲ (CN 1-May-2024)
Visible Particulates in Injections ⟨790⟩
Refractive Index ⟨831⟩
Specific Gravity ⟨841⟩
Specific Surface Area ⟨846⟩
Mid-Infrared Spectroscopy ⟨854⟩
Near-Infrared Spectroscopy ⟨856⟩
Ultraviolet-Visible Spectroscopy ⟨857⟩
Raman Spectroscopy ⟨858⟩
Thermal Analysis ⟨891⟩
Viscosity—Capillary Methods ⟨911⟩
Viscosity—Rotational Methods ⟨912⟩
Viscosity—Rolling Ball Method ⟨913⟩
Viscosity—Pressure Driven Methods ⟨914⟩
Characterization of Crystalline and Partially Crystalline Solids By X-Ray Powder Diffraction (XRPD) ⟨941⟩
Tablet Friability ⟨1216⟩
Tablet Breaking Force ⟨1217⟩
Water–Solid Interaction in Pharmaceutical Systems ⟨1241⟩
Applications of Nuclear Magnetic Resonance Spectroscopy ⟨1761⟩
Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections ⟨1787⟩
Visual Inspection of Injections ⟨1790⟩
Mid-Infrared Spectroscopy—Theory and Practice ⟨1854⟩
Near-Infrared Spectroscopy—Theory and Practice ⟨1856⟩
Ultraviolet-Visible Spectroscopy—Theory and Practice ⟨1857⟩
Raman Spectroscopy—Theory and Practice ⟨1858⟩
Rheometry ⟨1911⟩

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Topic/Question	Contact	Expert Committee
<1149> GUIDELINES FOR ASSESSING AND CONTROLLING THE PHYSICAL STABILITY OF CHEMICAL AND BIOLOGICAL PHARMACEUTICAL RAW MATERIALS, INTERMEDIATES, AND DOSAGE FORMS	Antonio Hernandez-Cardoso Senior Scientific Liaison	GCPA2020 General Chapters - Physical Analysis 2020
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	GCPA2020 General Chapters - Physical Analysis 2020

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