Drug Products, Including Biological Products, that Contain Nanomaterials

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Drug Products, Including Biological Products, that Contain Nanomaterials[1] Guidance for Industry[2]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Nanotechnology can be used in a broad array of FDA-regulated products, such as human drug products, including those that are biological products.[3] Nanotechnology may be used to create drug products in which nanomaterials (as explained in section II of this document), serve a variety of functions, for example as active ingredients, carriers loaded with an active ingredient, or inactive ingredients. The inclusion of such materials may result in product attributes that differ from those of products that do not contain such materials, and thus may merit particular examination. This document provides guidance on the development of human drug products, including those that are biological products, in which a nanomaterial is present in the finished dosage form.

Note that FDA does not categorically judge all products containing nanomaterials or otherwise involving the use of nanotechnology as intrinsically benign or harmful. Rather, for all products (nanotechnology-derived or otherwise), FDA considers the characteristics of the product and its safety and effectiveness for its use. FDA issued a guidance document to industry on the agency's considerations related to nanotechnology applications in FDA-regulated products

[1] This guidance document is one of several FDA guidance documents related to FDA-regulated products that may involve the use of nanotechnology. The use of the term "nanomaterial" in this document, as in other FDA guidance documents, does not constitute the establishment of a regulatory definition. Rather, we use this term for ease of reference only. See section II of this document for additional discussion.

[2] This guidance has been prepared by the CDER Nanotechnology Working Group in the Center for Drug Evaluation and Research (CDER) with participation from the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[3] Refers specifically to those drug products that are biological products under 42 USC 262(i) and subject to licensure under section 351(a) or (k) of the PHS Act (42 U.S.C. 262(a) or (k)). See 42 U.S.C. 262(j). According to 42 USC 262(i), the term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

(referred to as "FDA's nanotechnology considerations guidance").[4] FDA's consideration of the use of nanomaterials in drug products, including those that are biological products, in this document is consistent with FDA's nanotechnology considerations guidance, and with the broader federal guidance on regulatory oversight of emerging technologies[5] and nanotechnology.[6]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. SCOPE

This document provides guidance on the development of human drug products, including those that are biological products, in which a nanomaterial (as explained in this section) is present in the finished dosage form. This guidance focuses on considerations relevant to FDA's regulation of these drug products under the Federal Food, Drug, & Cosmetic Act (FD&C Act) and Public Health Service Act (PHS Act), and includes recommendations for applicants and sponsors of investigational, premarket, and postmarket submissions for these products.[7]

For purposes of this guidance:

- The term "drug product" or "drug products" hereafter refers to any human drug product or products in finished dosage form, including those that are also biological products, unless otherwise specified.
    - The term "biological products" refers specifically to those drug products that are biological products under 42 USC 262(i) and subject to licensure under section 351(a) or (k) of the PHS Act (42 U.S.C. 262(a) or (k)). See 42 U.S.C. 262(j).

[4] See FDA's guidance for industry *Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology*. For the most recent version of a guidance, check the FDA guidance web page at: https://www.fda.gov/scienceresearch/specialtopics/nanotechnology/default.htm.

[5] Office of Science and Technology Policy, Office of Management and Budget, and the United States Trade Representative. *Principles for Regulation and Oversight of Emerging Technologies*, March 2011; available online at:https://obamawhitehouse.archives.gov/sites/default/files/omb/inforeg/for-agencies/Principles-for-Regulation-and-Oversight-of-Emerging-Technologies-new.pdf.

[6] Office of Science and Technology Policy, Office of Management and Budget, and the United States Trade Representative. *Policy Principles for the U.S. Decision-Making Concerning Regulation and Oversight of Applications of Nanotechnology and Nanomaterials*, June 2011; available online at: https://obamawhitehouse.archives.gov/sites/default/files/omb/inforeg/for-agencies/nanotechnology-regulation-and-oversight-principles.pdf.

[7] This guidance also includes recommendations regarding NEPA, as relevant to potential FDA regulatory decisions on these drug products, but does not comprehensively address considerations that may be advisable to address compliance with legal obligations under other authorities, including those related to protection of occupational safety and health.

  - The term "drug product" also encompasses the drug or biologic constituent part of a combination product, as defined in FDA regulations at 21 CFR 3.2(e).[8]

- FDA has not established regulatory definitions of "nanotechnology," "nanomaterial," "nanoscale," or other related terms. As described in FDA's nanotechnology considerations guidance (issued in June 2014), at this time, when considering whether an FDA-regulated product involves the application of nanotechnology, FDA will ask:
  - (1) whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm).

  In addition, because materials or end products can also exhibit related properties or phenomena attributable to a dimension(s) outside the nanoscale range of approximately 1 nm to 100 nm that are relevant to evaluations of safety, effectiveness, performance, quality, public health impact, or regulatory status of products, we will also ask:
  - (2) whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm).

  We will apply these considerations broadly to all FDA-regulated products, including products within the scope of this guidance.

  For the purpose of this guidance only, we use the term "nanomaterial" generally to refer to materials falling within either point 1 or 2 above. The use of this term in this manner is consistent with its use in the FDA's nanotechnology considerations guidance. In addition, use of this term in this document is for the purpose of communicating FDA's current thinking elaborated in this document only.

- The term "application" refers to Investigational New Drug (IND) applications, New Drug Applications (NDAs), Biological License Applications (BLAs), Abbreviated New Drug Applications (ANDAs), and Drug Master Files (DMF), including any referenced DMF, unless noted otherwise.

This draft guidance does not apply to biological products composed of proteins, cells, viruses, nucleic acids, or other biological materials that naturally occur at particle sizes ranging up to 1 micrometer (1000 nm), such as gene therapy or vaccine products, unless a material that has been deliberately manipulated to have dimensions between 1-100 nm or to exhibit dimension-dependent properties or phenomena up to 1 micrometer, is also present in the product (e.g., as a carrier or an inactive ingredient). This draft guidance also does not apply to drug products that incidentally contain or may contain particles in the nanoscale range due to conventional manufacture or storage, in alignment with FDA's nanotechnology considerations guidance.[9]

[8] If the classification of a product as a drug, device, biological product, or combination product is unclear or in dispute, sponsors can contact the Office of Combination Products for assistance. See, e.g., guidance for industry and FDA staff *Classification of Products as Drugs and Devices and Additional Product Classification Issues.*

[9] However, evaluations of conventionally-manufactured drug products may include a consideration of effects, if any, of such incidental presence of particles in the nanoscale range on the safety or effectiveness of the product.

This draft guidance also does not apply to products not regulated by FDA as human drugs, for example, those regulated solely as drugs for animals, devices, foods, or cosmetic products.

This draft guidance discusses both general principles and specific considerations for the development of drug products containing nanomaterials, including considerations for establishing the equivalence of such products with other drugs. Considerations for quality, nonclinical, and clinical studies are discussed as they relate to drug products containing nanomaterials throughout product development and production. This draft guidance also includes recommendations on the specific content of applications for products containing nanomaterials where the nanomaterial is present in the finished dosage form.

Nonprescription drug products marketed under FDA's over-the-counter (OTC) drug monograph system (OTC monograph drugs) are not subject to premarket review and approval of product-specific marketing applications. Instead, among other requirements, such products must satisfy the conditions established in the applicable monograph (such as permitted active ingredients, dosage forms, and dosage strengths), must contain only safe and suitable inactive ingredients, and must be manufactured according to current good manufacturing practices.[10] If nanomaterials are present in a finished OTC drug product marketed under the OTC monograph system, its manufacturer is responsible for ensuring that the resulting product satisfies all applicable legal requirements. We therefore encourage monograph drug manufacturers to consider the general principles and specific considerations laid out in this draft guidance concerning drug development, safety evaluation, and quality considerations, and to consult with FDA to facilitate a mutual understanding of the specific scientific and regulatory issues for these products.

This guidance does not limit or classify the types of nanomaterials that can be used in drug products. Rather, it is focused on the deliberate and purposeful manipulation and control of dimensions to produce specific physicochemical properties which may warrant further evaluation with regards to safety, effectiveness, performance, and quality.

FDA does not address, or presuppose, what ultimate regulatory outcome, if any, will result for a particular drug product that contains nanomaterials. Issues such as the safety, effectiveness, public health impact, or the regulatory status of drug products that contain nanomaterials are currently addressed on a case-by-case basis using FDA's existing review processes. Current CDER and CBER guidance documents and requirements for the evaluation and maintenance of quality, safety, and efficacy, apply to drug products containing nanomaterials that otherwise fall within their scopes. As such, this guidance should be viewed as supplementary to other guidances for drug products. In addition, the Agency may continue to develop guidance addressing certain specific commonly-used types of nanomaterials, e.g., some liposomes,[11] to better address the challenges in evaluating and characterizing the quality and performance of drug products that incorporate them.

[10] 21 CFR 330.1; see generally 21 CFR part 330.

[11] See FDA's draft guidance for industry *Liposome Drug Products*. When final, this guidance will represent the FDA's current thinking on this topic.

III. RISK-BASED FRAMEWORK: POTENTIAL RISK FACTORS FOR PRODUCTS CONTAINING NANOMATERIALS[12]

There is great diversity in drug products containing nanomaterials including route of administration, indication, function of the nanomaterial, structural complexity, and maturity of the technology (including manufacturing processes, analytical techniques, and product design). In some instances, nanomaterials may take on different chemical, physical, or biological properties than their larger-scale counterparts that may impact quality, safety, or efficacy. For example,[13]

- Nanomaterials may have enhanced rates of dissolution and may improve bioavailability (BA) compared to the same material that is not manufactured to be a nanomaterial. In addition, after entry into the systemic circulation, nanomaterials can affect the distribution, the exposure-response profile, and the residence time of an active ingredient. These changes may be partly due to the interaction of nanomaterials with multiple plasma proteins resulting in the formation of a protein corona. The bound plasma proteins may endow nanomaterials with new biological properties. Through endocytosis the nanomaterial-protein complex can be taken up by tissue cells. Elimination of the nanomaterial-protein complex occurs mainly through phagocytosis by macrophages of the mononuclear phagocyte system, predominantly in the liver and spleen. Thus, nanomaterials enable targeting of active ingredients to specific sites but at the same time they may become targets of the complement and mononuclear phagocyte systems. Small hydrophilic nanomaterials may be eliminated by the kidney.

- Nanomaterials can be passively and/or actively targeted to different sites within the body. For example, passive targeting to different organs (e.g., liver) may be accomplished based on size or charge, while active targeting of tumors typically requires attachment of specific molecules (e.g., ligands, monoclonal antibodies, small molecules) to the surface of nanomaterials that are recognized by receptors on cancer cells.

Compared to other products, further understanding may be needed regarding the interactions of nanomaterials with biological systems. These interactions include, but are not limited to, the impact of intrinsic (e.g., disease, age, sex) and extrinsic factors (e.g., co-administered drugs) on exposure and response, the role of enzymes and transporters in their disposition, and their immunogenic potential.

This guidance is based on the premise that adequate (1) characterization of the nanomaterial, and (2) understanding of a nanomaterial's intended use and application, and how the nanomaterial attributes relate to product quality, safety, and efficacy, is a suitable framework for evaluating

[12] As explained in section II of this document, we use the term "nanomaterial" in this document for ease of reference. See FDA's guidance for industry *Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology* for more information.

[13] Tyner, KM et al. WIREs Nanomed Nanobiotechnol 2015. doi: 10.1002/wnan.1338; Tyner, KM et al. The AAPS Journal 2017. doi: 10.1208/s12248-017-0084-6; Cruz, CN et al. The AAPS Journal 2013. doi: 10.1208/s12248-013-9466-6; Palombo M, et al. Annu Rev Pharmacol Toxicol. 2014doi: 10.1146/annurev-pharmtox-010611-134615.

potential risk(s) associated with drug products containing nanomaterials. We propose a risk-based approach focusing on the following risk factors, which are further addressed in this guidance. Note this list is not comprehensive and other risk factors may need to be evaluated during product development. Development of drug products containing nanomaterials entails continual reduction of residual uncertainty throughout a product's lifecycle.

Factors for Assessment of the Nanomaterial:

- Adequacy of characterization of the material structure and its function.
- Complexity of the material structure.
- Understanding of the mechanism by which the physicochemical properties of the material impact its biological effects (e.g., effect of particle size on pharmacokinetic parameters).
- Understanding the in vivo release mechanism based on the material physicochemical properties.
- Predictability of in vivo release based upon established in vitro release methods.
- Physical and chemical stability.
- Maturity of the nanotechnology (including manufacturing and analytical methods).
- Potential impact of manufacturing changes, including in-process controls and the robustness of the control strategy on critical quality attributes of the drug product.
- Physical state of the material upon administration.
- Route of administration.
- Dissolution, bioavailability, distribution, biodegradation, accumulation and their predictability based on physicochemical parameters and animal studies.

IV. QUALITY: CHEMISTRY, MANUFACTURING, AND CONTROLS

A. Description of the Nanomaterial(s) in the Drug Product

A description of nanomaterials in the drug product should be included in the application, as part of the sections on product composition and description (e.g., common technical document (CTD) 3.2.P.2.1). The description of the nanomaterial should include information that sufficiently describes the product (e.g., size, charge, morphology, composition, and complexation) at a level appropriate for the stage of product development. At the IND stage, sufficient description of the nanomaterial is necessary to ensure safety during use in clinical trials as well as to collect sufficient data to bridge early development batches to late stage clinical trial material and the

proposed commercial material.[14,15] Sufficient description of the nanomaterial in an ANDA, NDA, or BLA allows for control over the material properties to ensure consistent quality of the drug product. A narrative description and a complementary diagram of the structure being described should be included. The description of the nanomaterial structure is particularly important for more complex structures involving multiple components or compartments (e.g., layers, core-shell structures), ligands, and coatings. Providing only an ingredient list may not be sufficient to explain the resulting structure of the nanomaterial after assembly, formulation, and/or processing.

In addition to the description of the nanomaterial structure, a description of the functionality of the nanomaterial should be included (e.g., used for solubilization of the active ingredient, as a carrier, as the active ingredient, for targeting and delivery).

FDA acknowledges that as product development progresses, more information will become available on the structure and function of the nanomaterial. For example, approximate values for nanomaterial particle size or coating thickness may be provided in the description portion during early stages of development. However, as the product enters late stage development (e.g., pivotal clinical and safety trials), the description of the material and understanding of the material functionality should be revised, as applicable, and supported with characterization data accordingly.

Generally, information on the structure of a specific nanomaterial can also be referenced with an appropriate letter of authorization to other applications or to a drug master file, as appropriate. However, as with any product, the applicant is responsible for the quality of all ingredients, [16] including nanomaterials used in the product, which may be challenging for highly complex structures.

B. Nanomaterial Quality Attributes and Structural Characterization

As with any formulation, a full description of the physical and chemical characteristics of the drug substance must be provided,[17] including proper characterization of identity, strength, stability, and quality of the product. The nanomaterial's critical quality attributes (CQAs) should be determined with regard to its function and potential impact on product performance. The nanomaterial properties that can impact product performance should be defined along with the potential risks due to changes in those properties, whether as final product quality attributes or as intermediate material attributes. The applicant should utilize risk assessments that link the structure-function relationship of the nanomaterial to attributes that need to be examined during development and controlled if changes are made during development of the final product formulation or manufacturing process.

[14] See FDA's guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products*.

[15] See FDA's guidance for industry *INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information.*

[16] See 21 CFR 314.50(d)(1)(ii)(a); 21 CFR 314.94(a)(9) (requiring, among other things, an ANDA to contain the information required under 2 CFR 314.50(d)(1)); 21 CFR 601.2.

[17] Ibid.

As with most aspects of the drug product development process, the specific CQAs for a nanomaterial will be product-specific and will most likely include a combination of attributes that are specific to the nanomaterial (e.g., particle size distribution and physical stability) and those that are not necessarily nanomaterial-specific (e.g., impurities). The sponsor should justify the level of nanomaterial characterization based on the impact of its quality attributes on the function of the drug product as well as the general knowledge of the nanomaterial published in the literature. The CQAs need not be an exhaustive catalogue of quality attributes, but should capture attributes that potentially impact the quality, safety, or efficacy of the final product.

The following attributes should be described and measured[18] for any nanomaterial in a drug product:

- Chemical composition;
- Average particle size;
- Particle size distribution (PSD) (description of d10, d50, d90 or polydispersity; modality);
- General shape and morphology (aspect ratio); and
- Stability, both physical (e.g. aggregation and agglomeration or separation) and chemical.

Additional quality attributes may also apply to nanomaterials in drug products, depending on the particular drug product (e.g., route of administration), its indication, and patient population. Examples can include, but are not limited to:

- Assay and distribution of any active ingredient associated with the nanomaterial and free in solution (e.g., surface bound or liposome encapsulated versus free active ingredient);
- Structural attributes that relate to function (e.g., lamellarity, core-shell structure);
- Surface properties (e.g., surface area, surface charge, chemical reactivity, ligands, hydrophobicity, and roughness);
- Coating properties, including how coatings are bound to the nanomaterial;
- Porosity (if it relates to a function, e.g., capacity to load a drug);
- Particle concentration;
- In vitro release;

[18] The methodology, sampling and testing frequency, and acceptance criteria for these attributes will depend on the control strategy considerations (review and inspection) for each product. Drug products containing nanomaterials should include information in the submission regarding the characterization and understanding of these attributes.

- Crystal form;

- Impurities; and

- Sterility and endotoxin levels.[19]

C. Nanomaterial Physicochemical Characterization Methods

Some standardized methods for nanomaterial characterization exist or are currently being developed (e.g., ISO 22412:2017, ASTM E2859-11(2017)). As with any method used in support of an application, adequacy for a standardized method should be demonstrated and justified for the product being tested (e.g., the particle size range or the presentation of the sample). In addition, corresponding validation and verification and related protocols should be provided as per FDA's guidance on methods validation.[20]

Sponsors should consider the following factors when selecting and using specific characterization methods:

- Method suitability: Sponsors should ask: (1) Is the method capable of detecting and characterizing the material in the size range of interest (e.g., laser diffraction versus light scattering, or various forms of microscopy)? (2) Does the methodology require a sample preparation that may significantly alter the nanomaterial attribute being measured during analysis (e.g., dilution, drying, or sonication)? (3) Can the analytical equipment have unintended interactions with the nanomaterial (e.g., filters)?

- Complementary methods: In some cases, several different analytical techniques may be available to characterize a given material attribute, for example particle size or morphology. Due to inherent differences in analytical techniques for measuring a given attribute, different instruments may provide different endpoint measurements. To address technique-related differences, we recommend the use of complementary methods when measuring material attributes that have been established as critical (e.g., use both dynamic light scattering and transmission electron microscopy for size). In addition, a description of what is being measured should also be provided (e.g., hydrodynamic radius versus projected radius, ensemble versus single particle results) in order to account for potential differences. If different techniques are needed -at different stages of processing (e.g., in-process, on final product release, and on stability), justification and any correlation of the measurement should be discussed. The analysis of raw data also needs to take into account the behavior of nanomaterials (e.g., diffusion).

  Sampling: Whenever possible, testing of the nanomaterial should be performed in a state that is most representative of the process stage being evaluated (e.g., in-process, isolated

[19] See FDA's guidance for industry *Pyrogen and Endotoxins Testing: Questions and Answers.*
[20] See FDA's guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics.*

intermediate, final formulation, during storage, and in-use conditions), taking into consideration how each process stage may impact quality.

- Sample preparation: Diluting or drying out a formulation or sample for analysis may produce substantial changes in the nanomaterial such that it is no longer representative of the nanomaterial contained in the final product. Therefore, any change made to the material from the original sample aliquot should be evaluated for relevance to the attribute being measured. Filtration steps may also confound results. Nanomaterials may interact with the filter medium, causing a loss of sample. Alternatively, in some methods a filtration step may lead to an erroneous conclusion that all material passing through the filter is in a dissolved state, because nanomaterials may pass through filters while remaining discrete entities (e.g., as nanocrystals instead of dissolved molecules). Therefore, the sample preparation steps for a nanomaterial should be adequately controlled to ensure these steps do not substantially change the product from its intended state.

In addition to the specific points above, additional general considerations for analysis include:

- Shape assumptions in analysis (e.g., assuming a sphere).
- Sufficient sample size (number of samples analyzed to ensure adequate statistical rigor).
- Appropriate reporting of results (e.g., cumulant analysis or distribution analysis; intensity, volume, or number weighted distributions; number or histogram for dynamic light scattering data).
- Appropriate use of viscosity in particle size measurements (e.g., dynamic viscosity or apparent viscosity).
- Sample preparation protocols (e.g., microscopy).

D. Dissolution/In Vitro Drug Release Methods for Quality Testing

A fully validated dissolution/in vitro release method is one of the control tools to ensure that quality and clinical performance are maintained throughout the lifecycle of the drug product. For example, in vitro release methods may aid in the characterization of liposome integrity, and in quantifying free versus encapsulated drug. Like drug products without nanomaterials, drug products containing nanomaterials should have dissolution/in vitro release methods capable of discriminating formulation and manufacturing differences which may impact the clinical performance of the drug product. In general, the dissolution/in vitro release testing should be conducted with the drug products manufactured under target conditions and compared to drug products that are intentionally manufactured with meaningful variations in formulation and manufacturing parameters, such as particle size, drug loading, types and/or amounts of inactive ingredients. Ideally, the dissolution/in vitro release method should be able to discriminate batches that are not bioequivalent to the pivotal clinical batch, which will have demonstrated efficacy and safety. Detailed descriptions of the proposed dissolution/in vitro release test and the

developmental parameters (selection of equipment/apparatus, media, agitation/rotation speed, pH, sink conditions, surfactant type and concentration) should be included in the submission. Drug release profiles should be complete; that is, drug release should reach a plateau (no significant increase over three consecutive time points) and achieve at least 85 percent release of the labeled amount of active ingredient(s), or, if not complete, the application should provide additional data to explain the reasons for incomplete release. As mentioned above, in vitro methods involving filtration that are used for testing during development and quality control (e.g., dissolution and assay) may need to be revised for appropriate use in the formulations containing nanomaterials. For example, using current United States Pharmacopeia (USP) dissolution methods that require filtration may lead to misinterpretation of results.

Due to the complex nature of some drug products containing nanomaterials, a sponsor may be motivated to develop a novel in vitro release/dissolution method for its product. If a sponsor develops novel drug release/dissolution methods, we recommend consultation with the Agency regarding feasibility, scientific rationale, and method validation to ensure that such a method is reproducible, reliable, and sensitive to variations in the product's formulation and manufacturing processes.

E. Manufacturing Process and In-Process Controls

All drugs , including both active ingredients and finished drug products that contain nanomaterials, must be manufactured in accordance with current good manufacturing practice (CGMPs) as set forth in section 501(a)(2)(B) of the Food, Drug, and Cosmetic Act (FD&C Act). In addition, the CGMP regulations in 21 CFR parts 210, 211, & 212, and the regulations in 21 CFR parts 600-680, as applicable, apply to finished drug products, including drugs subject to OTC monograph regulations. (See 21 CFR 330.1(a).) The variety of nanomaterials and their uses in drug products continue to grow. A comprehensive body of knowledge of nanomaterial attributes and the effects of these attributes on the quality and manufacturing process of drug products does not currently exist. Building a knowledge base to better understand potential risks to product safety, identity, strength, quality and purity characteristics during manufacturing of drug products containing nanomaterials is essential to establishing robust control strategies and implementing effective process validation protocols. It is, therefore, critical that the applicant apply manufacturing experience and increased understanding of potential risks to improve both the manufacturing process and associated control strategy over time.

Nanomaterials are engineered and manufactured to elicit novel product properties and clinical outcomes. The quality, safety, or efficacy of drug products containing nanomaterials can, however, be very sensitive to process conditions and production scales. Moreover, environmental controls should be established early in the development stage to prevent cross-contamination. This type of process and scale dependency, coupled with inherent polydispersity of some nanomaterials, makes it a priority to assess the risk to quality associated with the nanomaterial attributes, and develop adequate detectability of both nanomaterial and process failures at the development stage. As such, the earlier that CQAs can be identified during development, the more quickly in-process controls can be designed and implemented in the manufacturing process. A well-disciplined design control approach can generate key process knowledge, especially for those areas where, in the absence of comprehensive understanding,

variability is not predictable, scale effects are unknown, and where results cannot be extrapolated or interpolated to demonstrate safety and efficacy.

A different shape or size of a nanomaterial could be considered a batch consistency issue if it impacts the quality, safety, or efficacy of the product. In addition, nanomaterial carriers (i.e., a carrier that is a nanomaterial) that are empty or have missing or incomplete surface coatings could be considered an impurity and may need to be quantified.

For drug products containing nanomaterials, changes in analytical methods, manufacturing process, scale, and manufacturing sites may make the bridging of early development lots to large commercial scale lots difficult. It is important to ensure that a sufficient amount of product is retained from all batches to allow any future analysis by updated or complementary methods. This will help to establish a bridge between developmental and commercial batches. This applies to stability samples as well as stable process intermediates.

F. Excipients

1. Function

Nanomaterials can be present as excipients in drug products and may serve specific functions to ensure or enhance desired product attributes. For the purposes of this guidance, an excipient is any inactive ingredient that is intentionally added to a therapeutic or diagnostic product, but that is not intended to exert therapeutic effect(s) at the intended dosage, although it may act to improve product delivery (e.g., enhance absorption or control release of the drug substance). For example, nanomaterial excipients can be used as adjuvants for vaccines or for delivery of antigens or genetic material. Excipients (e.g., polymers, targeting agents, coating agents, and lipids) are also used as matrices to assemble structures or to stabilize more complex nanomaterials. The material attributes of these excipients are a critical element of the control strategy relating to product performance. For example, the purity of lipids used in a liposome or the molecular weight distribution of the polymers used in nanomaterial drug delivery systems may be critical. Therefore, nanomaterial excipient properties need to be fully characterized based on their functionality and intended use. Proper controls, including test methods and acceptance criteria, a description of material source, and grade should be defined in an application, with justification for how those acceptance criteria enable the product to meet its desired quality target product profile. Changes in the grade and source of nanomaterial excipients during development should be addressed with regard to how these changes may impact the safety or efficacy of the product.

Some nanomaterials (whether as primary particles or in an agglomerated or aggregated state) are commonly used as excipients (e.g., diluents, surfactants, glidants, emulsifiers, and lubricants), to improve processability and formulation performance. As a general matter, nanomaterial excipients with documented prior human exposure under circumstances relevant to the proposed use (including the same route of administration, dosage forms, function, and maximum potency) can be adequately described in terms of the excipient's overall function and control specification, the same as other commonly used excipients. These common nanomaterials may represent a low

risk to product safety and efficacy; however, excipient functionality may still be important for overall product quality.

2. Safety

The incorporation of an excipient into a nanomaterial structure or reducing the size of an excipient below 1 micrometer (1000 nm) may have implications for the safety and/or efficacy of the finished product. Current FDA guidance on evaluating the safety of new excipients[21] applies when a common excipient is deliberately modified into a nanomaterial. An adequate safety evaluation should be provided when the nanomaterial's safety is not fully demonstrated by existing safety data with respect to level of exposure, duration of exposure, and route of administration. In the event that a common excipient has been deliberately modified to be a nanomaterial or incorporated into a nanomaterial, we recommend that you consult with the Agency regarding any impact on potential exposure to and safety of the material.

G. Stability

Current FDA guidance documents related to the extent of stability data and testing conditions to support drug product applications[22] applies to drug products containing nanomaterials. The determination of container closure system suitability, storage conditions, shelf life, and in-use conditions for a drug product containing nanomaterials will be based on chemical and physical stability of that product, as justified by data, consistent with current FDA guidance on this issue.

In particular, when assessing the stability of the drug product, the developer should consider potential factors impacting the product performance, including interactions of nanomaterial properties, prior to reaching the patient. The study of the stability of nanomaterials in products should involve the evaluation of physical and chemical changes in the material during handling and storage. There are particular risk factors that are more specific to the physical stability of nanomaterials. Stress stability studies can be useful in elucidating changes and pathways of those changes in the nanomaterials. Stability issues that impact nanomaterial properties may include, but are not limited to:

- Changes to particle size and size distribution.
- Changes to particle morphology.
- Self-association (agglomeration/aggregation).
- Change in surface charge (e.g., zeta potential).
- Changes in dissolution/release rate of active ingredient.

[21] See FDA's guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*.

[22] See FDA's guidances for industry *ICH Q1A(R2) Stability Testing of New Drug Substances and Products; ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products; ANDAs: Stability Testing of Drug Substances and Products;* and *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers.*

- Drug leakage from a nanomaterial carrier.

- Degradation of particle (e.g., removal/exchange of surface ligands).

- Interaction with formulation or container closure (e.g., compatibility, denaturing of proteins).

- Changes to reconstitution properties of the product.

- Changes in the solid state (e.g., crystal structure).

In addition, if the drug product must be diluted prior to use, the dilution medium may affect surface charge and/or particle size, altering colloidal stability of nanomaterials and triggering release of the active ingredient. In-use stability studies at clinically relevant concentrations and under relevant storage conditions may also be requested. Such studies may evaluate nanomaterial interactions with surfaces in the primary package, since these can result in changes to CQAs. Note that stability issues during storage can include interaction with the storage container, contact with administration or delivery devices (e.g. syringe walls, catheters), and dispersion media.

H. Postmarket CMC Changes

Additional risk factors may arise when making a major or moderate change[23] to drug products containing certain nanomaterials after approval. The comparison between a drug product before a change and after a change may require physicochemical comparison of CQAs and may require in vivo bioequivalence (BE) studies, depending on the impact of the change and the type of product.[24] As stated above, retention of samples from pivotal batches through development to enable bridging between manufacturing process changes, scale-up, and site transfers may be a

[23] See 21 CFR 314.70(b) &(c) (classifying as major changes and moderate changes, respectively, changes in the drug substance, drug product, production process, quality controls, equipment, or facilities that have substantial potential (for major changes) or moderate potential (for moderate changes) "to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product"). Such changes require supplemental applications prior to implementation. See 21 CFR 314.97 (changes to approved ANDAs also subject to 21 CFR 314.70, see also 601.12 (regulation defining and governing changes to licensed biological products).

[24] For general information/examples of change categories, see the following FDA guidances for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation;* and *SUPAC-SS: Nonsterile Semisolid Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation;* and *Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation;* and *ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process.*

suitable strategy. For manufacturing changes that may affect the bioequivalence of certain drug products containing nanomaterials, please refer to section VI of this guidance.

V. NONCLINICAL STUDIES FOR DRUG PRODUCTS

A. General Applicability of Existing Guidance

All existing International Conference on Harmonization (ICH) guidance addressing nonclinical safety of drug products and their components is generally applicable to drug products containing nanomaterials. New drug products that contain nanomaterials should be thoroughly tested as for any new drug product. However, depending on the water solubility of the component or aggregation under in vitro conditions, some in vitro assays may not be appropriate, or the conditions under which these assays are conducted might need to be adjusted.

B. Absorption, Distribution, Metabolism, and Excretion (ADME) Considerations

Components that are nonbiodegradable can accumulate and persist longer than biodegradable components and can consequently produce effects related to chronic exposure to these components. A nanomaterial can sometimes cross biological barriers in greater amounts than the larger particle size version. This can lead to increased safety concerns in some cases, such as increased penetration of the blood-brain barrier, or the placenta.[25] If a drug product contains nanomaterials as excipients, including excipients that function as drug carriers, the biological fate of the carriers and their potential impact on safety may need to be determined in addition to those of the active ingredient.

To conduct biodistribution studies of nanomaterials, it may be necessary for the material to be labeled in some manner (e.g., radiolabeled, fluorescence). Data should be collected demonstrating that the label does not substantially affect the biodistribution of the nanomaterial.

C. Risk Considerations for Specific Routes of Administration

The following route-specific issues should be considered when assessing the safety of a drug product containing nanomaterials, and may warrant special assessment in addition to the nonclinical studies normally conducted in support of drug product development.

1. Topically Applied Products

Increased hair follicle penetration or distribution to local lymph nodes is a possibility for nanomaterials.[26] In addition, nanomaterials can interact with sunlight differently than larger size

[25] Pietroiusti, A et al. Small 2013. doi: 10.1002/smll.201201463; Landsiedel, R et al. Arch Toxicol. 2012. doi: 10.1007/s00204-012-0858-7; Hubbs, AF et al. Toxicol Pathol. 2011 Feb;39(2):301-24. doi: 10.1177/0192623310390705.

[26] Gulson, B et al. Arch Toxicol 2015. DOI 10.1007/s00204-015-1564-z.; Almeida, JP et al. Nanomedicine (Lond). doi: 10.2217/nnm.11.79.

particles and this can impact the interaction of light with the skin. Penetration of a nanomaterial through the skin in human patients can be impacted by the condition of the skin (e.g., intact, damaged, diseased). The evaluation of effects and exposures achieved in the nonclinical studies should consider this impact.

2. Subcutaneous Administration

Materials introduced below the stratum corneum can possess an increased sensitization potential compared to some other (e.g., dermal) routes. It has been reported that nanomaterials injected subcutaneously can enhance sensitization to other allergens.[27] The biological fate of non-soluble nanomaterials should be considered.

3. Inhalation

Local/respiratory toxicity of nanomaterials can differ from larger particles, as can lung deposition, distribution in respiratory tissues, and systemic BA.[28] The biological fate (accumulation/translocation) of non-soluble carrier nanomaterials should be considered.

4. Intravenous Products

Drug products containing nanomaterials can have a different tissue distribution of the active ingredient and a different half-life compared to the same drug products without nanomaterials. Changes in hemocompatability can occur.[29]

5. Oral Products

For orally administered drug products, use of nanomaterial ingredients is often intended to increase bioavailability of the active ingredient. Other than possible local effects and an increased absorbed dose (which should be detected with existing methods), if the oral toxicology studies with a micrometer scale material were adequate, new effects are not expected for soluble drugs. If an insoluble nanomaterial is included in an oral product, toxicology studies should take this into consideration and include assessment of tissues where such materials might accumulate.

D. Testing of Representative Nanomaterial

Before toxicity studies are conducted with a drug product containing nanomaterials, it is important to know that the nanomaterial has been made reproducibly and that it is representative of the nanomaterial to which humans will be exposed. The different factors, vehicles, and media that affect the aggregation and surface properties of the drug, in vitro and in vivo, should be understood. Appropriately validated analytical methods should be used to characterize the test articles used in nonclinical studies. These analytical methods should include methods suitable

[27] Dobrovolskaia, MA et al. Nat Nanotechnol 2007. doi: 10.1038/nnano.2007.223; Ilinskaya, AN et al. Toxicol Appl Pharmacol 2016. doi: 10.1016/j.taap.2016.01.005; Smith, AR et al. Curr Allergy Asthma Rep. 2017 doi: 10.1007/s11882-017-0674-5.

[28] Stone, V et al. Environ Health Perspect. 2016. doi: 10.1289/EHP424.

[29] See footnote 11.

for the unique properties of nanomaterials, as discussed elsewhere in this guidance (section IV), when test articles contain nanomaterials.

Generally, nonclinical evaluations of the kind typically conducted to support development of any drug product will be adequate to assess drug products containing nanomaterials when the clinical material is tested in the nonclinical studies. However, as noted above, some in vitro assays may not be appropriate for drugs that contain nanomaterials, or the conditions under which these assays are conducted might need to be adjusted in order to obtain accurate results.

E. Bridging Toxicology from a Drug Product not Containing Nanomaterials to a Drug Product Containing Nanomaterials

When a previously-approved drug product is modified to include a nanomaterial (active ingredient or inactive ingredient), ADME and a bridging toxicology study can often be appropriate and sufficient to allow reliance on previous nonclinical information assuming other regulatory requirements are met. Consideration should be given to how the change may affect drug ADME and what potential impact any change may have on toxicity, e.g., increased penetration through the placenta (refer to section V.B). Additional studies can be warranted if changes suggest the possibility of an altered effect in a particular tissue. In some cases, when the nanomaterial is not the active ingredient, assessment of its contribution to any observed toxicity can be useful in interpreting such bridging studies. Therefore, inclusion of treatment groups with only the nanomaterial should be considered.

VI. CLINICAL DEVELOPMENT

The clinical development of drug products containing nanomaterials should follow all policies and guidances relevant to clinical safety and efficacy studies as they pertain to development of IND, NDA, ANDA, and BLA submissions. This section addresses the particular topic of clinical development of drug products containing nanomaterials developed using a reference product, e.g., along the 505(b)(2), 505(j), and 351(k) pathways.

A. 505(b)(2) Submissions

1. General Considerations

From a pharmacokinetic-pharmacodynamic (PK-PD) point of view, drug products that contain nanomaterials can be differentiated into two different types: (1) those where the nanomaterial is the active ingredient, or (2) those where the nanomaterial carries the active ingredient solubilized, conjugated, associated, or encapsulated for delivery. For the first type, determination of PK and PD is focused on the active ingredient as the nanomaterial. For the second type, determination of PK and PD is focused on the released active ingredient and the PK of the carrier. An example for the first category is a stabilized nanocrystal suspension. Examples of the second category include liposomes, polymeric nanoparticles, and dendrimers. Note that nanomaterial carriers may exhibit inherent biological activity that is not related to the

loaded active ingredient (e.g., immunogenicity) and could also affect the safety and effectiveness of the drug product.

The disposition and exposure-response relationship of an active ingredient formulated as a nanomaterial (whether a nanomaterial itself or within a nanomaterial carrier) may not be the same as for a drug product that does not contain nanomaterials. Nanomaterial carriers can deliver the active ingredient to the target tissue by various routes, such as the endocytic route or via enhanced permeation retention (EPR) effect. Consequently, the tenet for products containing the same active ingredient, i.e., that equivalent active ingredient exposure in plasma ensures equivalent therapeutic performance, may not hold for proposed drug products containing nanomaterials relative to a reference drug product that does not contain nanomaterials. In some cases, demonstration of BE between a proposed product containing nanomaterials and a referenced product (whether or not the referenced drug product also contains nanomaterials) may not be sufficient to bridge the proposed product to the referenced product. Additional nonclinical and clinical evidence may be required to demonstrate comparable disposition and exposure-response relationship for the active ingredient between a proposed product containing nanomaterials and a referenced product. For example, if the goal of a development program for a drug product containing nanomaterials developed along the 505(b)(2) path is to demonstrate no clinically meaningful difference in disposition and exposure-response relationship relative to the reference product, the magnitude of the development program depends on the amount of evidence required to support this demonstration or bridge.

In development programs attempting to bridge the performance of a drug product containing nanomaterials to a referenced drug product, FDA recommends that sponsors apply a risk-based approach to determine if the product in development will exhibit clinically significant changes in exposure, safety, and/or effectiveness relative to the referenced product. The risks of a drug product exhibiting such clinically significant changes may vary; factors that can influence that risk include certain characteristics of the nanomaterial contained within the drug product, route of administration, and frequency of use. With medium and high risk drug products containing nanomaterials, the residual uncertainty about equivalent exposure indicating equivalent therapeutic performance is greater than with low risk drug products containing nanomaterials. To reduce the residual uncertainty with medium and high risk drug products containing nanomaterials, the exposure-response profile may have to be explored. In addition, a particular drug product may be considered higher or lower risk for bridging based on other clinical or safety information. Such considerations should be demonstrated in development programs attempting to bridge the performance of a drug product containing nanomaterials to a referenced drug product.

Below, we present examples that are meant to be illustrative of the risk categories, derived from the Agency's preliminary thinking and experience with drug products containing nanomaterials. Note that these examples are not comprehensive.

- *Low risk to exhibit clinically significant changes in exposure, safety, and/or effectiveness relative to the referenced product*: For example, drug products containing nanomaterials that revert to their molecular constituents immediately after administration are likely to present low risk, whether these drug products are administered by oral, topical, and

parenteral routes. Examples include oral nanocrystals and some intravenous lipid nanoparticles.

- *Medium risk to exhibit clinically significant changes in exposure, safety, and/or effectiveness relative to the referenced product*: For example, drug products containing non-targeted nanomaterials intended for systemic action that are administered parentally are likely to present medium risk. Examples include drug products with known or predictable active ingredient release characteristics.

- *High risk to exhibit clinically significant changes in exposure, safety, and/or effectiveness relative to the referenced product*: For example, drug products containing targeted nanomaterials intended for systemic action and that are administered intravenously are likely to present high risk. Examples include drug products with complex and difficult to predict active ingredient release characteristics.

2. Clinical Studies

In the clinical development of drug products that follow a 505(b)(2) approval pathway and are low risk, demonstration of BE between the proposed and the referenced product based on a comparative plasma PK may be generally sufficient to bridge. Products in the medium and high risk categories should initially include single and multiple dose studies assessing PK, PD, and tolerability to characterize the proposed product. These studies should be followed by a single dose BE study comparing the proposed and the referenced product. For orally administered nanomaterials, a single dose fed BE study is also necessary to provide a sufficient bridge.

For medium and high risk drug products containing nanomaterials, demonstration of BE between the proposed and the referenced product alone may not be enough to ensure therapeutic equivalence, and additional evidence for comparability of disposition and exposure-response relationship of the active ingredient across test and referenced products may be necessary. The extent of evidence needed to demonstrate comparable therapeutic performance in addition to BE with the referenced product is potentially greatest for high risk products.

For medium and high risk drug products containing nanomaterials that are proposed to be bioequivalent to the referenced drug product, a single dose comparative ADME study can provide additional assurance of similarity of disposition of the active ingredient with the referenced product. However, ADME studies may not be able to detect discrete but clinically significant differences between products in rate and extent of release of the active ingredient into the target tissues. Single and multiple dose studies examining the PK and PD characteristics of the proposed product and the referenced product may be better suited because they allow an exploration of the exposure-response relationship. Both therapeutic- and toxicity-related PD biomarkers, ideally related to clinical outcomes, should be selected in these studies. Recognition of a difference in the exposure-response relationship between the proposed drug product containing nanomaterials and the referenced product may be facilitated if the selected PD biomarkers vary over the blood/plasma concentration range of interest and exhibit a reasonably rapid onset and offset of the response.

If PD biomarkers suitable for establishing comparative exposure-response relationships are not available, the development program of drug products containing nanomaterials may have to include comparative safety and effectiveness studies. Specific safety or effectiveness concerns regarding the referenced drug product and its pharmacological class also may necessitate additional comparative clinical safety and effectiveness data for drug products containing nanomaterials. Clinical studies may be designed to demonstrate that the proposed drug product containing nanomaterials does not have decreased activity compared to the referenced product, as decreased activity usually would preclude approval. Alternatively, a superiority design may be used if the sponsor wishes to make a superiority claim over the referenced product. A study employing a sequential test in which non-inferiority is tested first and superiority is tested second may be a useful design if a sponsor believes its drug product containing nanomaterials provides an efficacy advantage over the listed product. This study should be based on a pre-specified non-inferiority margin that is scientifically justified and adequate to enable the detection of clinically meaningful differences in effectiveness and safety between the proposed product and the referenced product.

A sponsor may use endpoints that are different from those in the referenced product's clinical trials if they are scientifically justified. For example, response rate may be an appropriate endpoint for a non-inferiority trial in the oncology setting where the referenced product was approved based on a progression-free survival endpoint. Certain endpoints that are effectively PD biomarkers, as discussed above, also may be acceptable.

The sponsor of a proposed drug product containing nanomaterials may seek approval only for indications that have been previously approved for the referenced product, unless new clinical trials to demonstrate safety and efficacy are conducted in the proposed new indication. Furthermore, extrapolation to other indications for the listed product also will necessitate new comparative clinical studies.

B. 505(j) Submissions

An applicant may seek approval of a generic product that references a drug product containing nanomaterials by submitting an ANDA under section 505(j) of the FD&C Act. An ANDA applicant must demonstrate, among other things, that the generic drug product is bioequivalent to the reference listed drug (RLD) (section 505(j)(2)(A)(iv) of the FD&C Act).[30] In addition, an ANDA must contain sufficient information to show that the proposed generic drug has the same active ingredient(s), previously approved conditions of use, route of administration, dosage form, strength, and (with certain exceptions) labeling as the RLD (section 505(j)(2)(A) and (j)(4) of the FD&C Act). Like all generic drug products, generic drug products containing nanomaterials meet the following general criteria: (1) they are approved as safe and effective, (2) they are pharmaceutically equivalent, (3) they are bioequivalent, (4) they are adequately labeled, and (5)

[30] Under the FD&C Act, "[a] drug shall be considered to be bioequivalent to a listed drug if . . . the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar does of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses." See section 505(j)(8)(B)(i); see also implementing regulations at 21 CFR part 320.

they are manufactured in compliance with CGMP regulations.[31] BE studies are conducted with the goal of demonstrating the generic drug has the same rate and extent of absorption at the target site as the RLD (21 CFR 320.1(e) and (f), 320.21(b)(1)). Nanomaterials range from simple nanocrystals, organic nanomaterials (e.g., liposome, polymeric nanoparticle) and inorganic nanomaterials (e.g., gold nanoparticles), to complex-structure integrated nanoparticles (e.g., core-shell, surface modified nanoparticles). Any critical structural change in the multiple components of nanomaterial-based products can influence the bioequivalence, pharmacology, and toxicology profiles. Due to the diversity of nanomaterial formulation, drug release mechanisms, and unique bio-distribution, evidence of comparable PK parameters in blood/plasma in conventional BE studies alone may or may not be sufficient to establish BE of the generic and the RLD depending on the route of administration and nanomaterials employed.

For orally-administered drug products containing nanomaterials that have relatively low risk, PK studies in blood/plasma and bioequivalence criteria generally are considered sufficient to demonstrate BE between the generic and the RLD. ANDA applicants using for their generic drug a nanocrystal similar to that used in the RLD can refer to FDA's draft guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*[32] for advice on BE study design. Generally, both fasted and fed BE studies are recommended to demonstrate BE of orally administered drug products.

ANDAs referencing oral drug products using nanotechnology to improve BA for poorly water-soluble drugs need not use that particular nanotechnology or any nanotechnology, but may use alternative strategies to achieve the same BA enhancement. There are a number of effective technologies that exist to improve drug BA, including the use of amorphous solid dispersions, introduction of surfactants or co-solvents, and others. If the ANDA applicant uses a different type of nanomaterial than the RLD (e.g., nanocrystal versus nanomaterials other than nanocrystals) that may potentially affect nanoparticle distribution in the GI tract, additional characterization and evidence supporting non-specific drug uptake by Peyer's patch or other GI tissues, should be provided.

For parenteral products containing nanomaterials, the applicant should demonstrate that the generic product contains the same active and inactive ingredients as the RLD (i.e., is qualitatively the same (Q1)) in the same concentration (i.e., is quantitatively the same (Q2)) as the RLD.[33] In general, the generic applicant should conduct in vivo BE studies, demonstrate comparable size and distribution of nanomaterials based on population BE criteria, and demonstrate sameness in a wide range of physicochemical properties.

There are significant challenges to demonstrating Q1 and Q2 sameness as well as BE between a generic parenteral drug product containing nanomaterials and its RLD. Firstly, the active ingredients of some nanomaterials are generally heterogeneous mixtures which may require

[31] Orange Book, Preface, Section 1.2 (pg. vii).

[32] When final, this guidance will represent the FDA's current thinking on this topic.

[33] Differences in preservatives, buffers, or antioxidants may be permitted provided that the applicant identifies and characterizes these differences and provides information demonstrating that the differences do not affect the safety or efficacy profile of the proposed generic drug product. See 21 CFR 314.94(a)(9)(iii).

considerable characterization to demonstrate drug substance sameness. Some critical excipients for the formation of nanomaterials are also complex. Secondly, the manufacturing processes for certain nanomaterials are complicated and involve lengthy steps. Thirdly, after administration, the drug substance often exists in multiple forms, e.g., free drug[34] or nanomaterial-associated drug, both in systemic circulation and at the target site. Therefore, it is critical to identify the most therapeutically relevant moiety for establishing BE. Furthermore, drug levels in systemic circulation may not always reflect drug concentration at the target site. As a result, in most cases, evidence of comparable PK parameters in blood/plasma in conventional BE studies alone may not be sufficient to satisfy the requirements for generic drug approval.

As for the most therapeutically relevant moiety for establishing BE, the ANDA applicant is advised to provide concentration-time curves for all clinically relevant entities (e.g., free drug and nanomaterial-associated drug) relating to the drug release from nanoparticles, in order to enable an accurate assessment of the PK of the generic product. The PK of both the free drug and nanomaterial-associated drug in the blood/plasma needs to be equivalent between the generic and the RLD, based on adequate and validated bio-analytical methods.

For generic parenteral drug products containing nanomaterials, since comparable PK parameters in blood/plasma alone may not be sufficient, additional measures such as comparative physicochemical testing would be needed to correlate the blood/plasma PK to its availability at the site of action. These physicochemical characterizations include particle morphology, particle size and distribution, surface property, free and nanomaterial-associated drug, and others. These in vitro characterizations should be conducted on at least three different batches of each of the generic and referenced drug products and analyzed by appropriate statistical methods (e.g., population equivalence for particle size distribution).

In general, an ANDA applicant is responsible for providing sufficient scientific evidence based on a comprehensive in vivo PK evaluation and in vitro physicochemical characterization to demonstrate the equivalence between generic and referenced nanomaterials. In addition, comprehensive characterization of the RLD and understanding of the fundamental chemistry used to form the active ingredient is needed to demonstrate equivalence. For the active ingredient, FDA considers an active ingredient in a generic drug product to be the same as that of the RLD if it meets the same standards for identity. The standards are based on USP standards or an evaluation of current data and other relevant scientific information, including characteristics of the RLD and scientific experience and expertise. Therefore, comprehensive characterizations of the RLD and understanding of the fundamental chemistry used to form the active ingredient would be needed for FDA to make its evaluation to establish appropriate standards.[35]

[34] As used in this guidance, free drug is drug not associated with a nanomaterial or nanomaterial carrier. Free drug may have been released from a nanomaterial carrier or never associated with a nanomaterial or nanomaterial carrier. Although not used in this sense in this guidance, in other contexts, "free drug" may refer to non-protein bound drug in the blood (PK).

[35] See FDA's draft guidance for industry *Bioanalytical Method Validation*. When final, this guidance will represent the FDA's current thinking on this topic.

The potential multi-component structure of drug products containing nanomaterials allows great flexibility of drug delivery designs. Due to the complexity and diversity of materials, structures, and functionalities of nanomaterials, the Office of Generic Drugs (OGD) currently examines nanoparticle-based parenteral drug products and develops product-specific BE guidance on a product-by-product basis.[36] A number of product-specific guidances, including BE recommendations for doxorubicin hydrochloride liposomal injection, sodium ferric gluconate colloidal complex, and others have been published.

C. 351(k) Submissions

The development of a biosimilar to a reference biological product containing nanomaterials should follow current guidance on biosimilars.[37] The contribution of the nanomaterial to product safety, purity, and potency would be assessed as part of the product development and the demonstration of biosimilarity or interchangeability. Sponsors are encouraged to contact FDA early during the development of biosimilars containing nanomaterials.

D. Bioanalytical Methods

All clinically relevant entities, i.e., parent drug and major active metabolites, if possible, should be measured in the appropriate biologic matrices after administration of products containing nanomaterials. In general, total, free, and nanomaterial-associated drug should be measured separately or indirectly derived. This may require separation of free and nanomaterial-associated drug prior to detection or simultaneous analysis. The concentrations of free parent drug and major active metabolite(s) may be low. The use of validated, specific, and highly sensitive methods is recommended.

E. In Vitro Tests With Human Biomaterials

Stability and Biocompatibility: The impact of human plasma and blood on the stability of nanomaterials intended for systemic activity and the biocompatibility of nanomaterial with blood and serum should be examined.

Because of significant differences between products containing nanomaterials and other products, the methods for the test procedures listed below may have to be appropriately adapted to provide reliable results with products containing nanomaterials.

Plasma Protein Binding: Nanomaterials entering the blood circulation interact with multiple plasma proteins in a process lasting over several hours, which ultimately results in the formation of a protein corona. The goal of this study, therefore, is to determine the major binding proteins involved in the formation of the corona over time and the percentage of bound nanomaterial over the incubation time.

[36] See *Product-Specific Recommendations for Generic Drug Development* at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[37] See a sortable listing of Biosimilarity guidances at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm290967.htm.

In Vitro Clearance and Metabolism: Phagocytes play a major role in the clearance of systemically administered nanomaterials. The uptake of nanomaterials may expose phagocytes to high concentrations of the active component. Therefore, in vitro exposure of cultured human phagocytes to nanomaterials may be useful in evaluating potential cytotoxicity. Small molecule active ingredients released from carriers are metabolized primarily by Phase 1 and Phase 2 enzymes or eliminated unchanged in the urine. The interaction of active ingredients that are nanomaterials and intact nanomaterial carriers with enzymes is thought to be limited, but some dissociated monomers such as block copolymers, PEG, and lipids may affect the function of cytochrome P450 enzymes and gastrointestinal transporters. Therefore, experimental evidence supporting or rejecting this notion should be provided.

F. Immunogenicity

There is a potential for nanomaterials to exert an immunogenic effect depending on a patient's immunologic status, prior history, route/dose/frequency of drug administration, and unique characteristics of the administered nanomaterial.[38] It is recommended that applicants use a risk-based approach to evaluate and mitigate adverse immune responses that may be associated with administration of products containing nanomaterials that could affect safety and efficacy. The risks for immunogenicity will need to be assessed on a case-by-case basis and considered at the earliest stage of product development as well as throughout the remainder of the product lifecycle depending on the potential severity of immune responses and the likelihood of their occurrence. Immunogenicity risks should similarly be assessed prior to implementing changes to the process and/or product (e.g., product and/or process optimization) depending on the extent of such changes and the level of risk for invoking immune responses. For general recommendations regarding how to evaluate and mitigate risks associated with adverse immune responses the applicants should consult FDA guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* and the ICH guidance *S8 Immunotoxicity Studies for Human Pharmaceuticals* for sample approaches. Immunogenicity risk assessments of biological products that have a non-biologic nanomaterial component should consider that the nanomaterial component may possess adjuvant properties. Consequently, biological products with a nanomaterial component may have different immunogenic characteristics compared to the biologic alone that may warrant specific examination.

VII. ENVIRONMENTAL IMPACT CONSIDERATIONS

The National Environmental Policy Act (NEPA) requires Federal agencies to assess the environmental impact of Agency actions and to ensure that the interested and affected public is informed of environmental analyses. FDA requires applicants to submit an Environmental Assessment (EA) or a claim of categorical exclusion when requesting Agency action on a drug or biologic application (21 CFR 25.15(a); see also, FDA's guidance for industry *Environmental Assessment of Human Drug and Biologics Applications*). In light of the current, evolving state of scientific knowledge regarding the impact of nanomaterials in the environment, CDER and CBER intend to use a case-by case-approach at this time to determine whether drug products that contain nanomaterials qualify for an existing categorical exclusion or whether an EA is required.

[38] See footnote 27.

In accordance with FDA regulations, if an EA is submitted, CDER or CBER will evaluate the information contained in the EA to determine whether it is accurate and objective, whether the proposed action may significantly affect the quality of the human environment, and whether an Environmental Impact Statement (EIS) will be prepared. If significant effects requiring the preparation of an EIS are identified, FDA will prepare an EIS for the action pursuant to its procedures (21 CFR 25.15(b)). If significant effects requiring the preparation of an EIS are not identified, resulting in a decision not to prepare an EIS, FDA will prepare a Finding of No Significant Impact, in accordance with 21 CFR 25.41.

To assist the Agency in our decision-making and help avoid late cycle information requests, we advise industry to notify the FDA early in the development process of their intent to either claim a categorical exclusion or submit an EA. Information supporting the criteria for the selected categorical exclusion and a statement of "no extraordinary circumstances" (see 21 CFR 25.21) should be provided. For example, the applicant could provide information demonstrating negligible release of the nanomaterial into the environment (e.g., dosing, ADME, partitioning and biodegradation data) or information demonstrating that the nanomaterial would not be expected to produce toxicity in aquatic and terrestrial organisms at expected levels of exposure. As needed, the Agency may request additional information to support a conclusion that approval of the application would not significantly affect the quality of the human environment. If FDA determines that extraordinary circumstances exist, the applicant will be required to submit an EA that assesses the exposure, fate, and effects of the nanomaterial(s) in the environment. If FDA determines that the proposed action may significantly affect the quality of the human environment and, therefore, prepares an EIS, FDA may request additional information from the applicant to assist in preparation of such an analysis. Impacts on the environment may occur at various stages of the product lifecycle, including manufacture, storage, patient use, and disposal.

FDA may provide additional guidance as needed and as our knowledge of and experience with nanomaterials increases.