
OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

**REVIEW OF ONADE REGULATED PRODUCTS THAT CONTAIN NANOMATERIALS
OR OTHERWISE INVOLVE THE USE OF NANOTECHNOLOGY**

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I. PURPOSE

This document provides:

- points to consider in identifying products containing nanomaterials or involving the application of nanotechnology
- a means to collect information and establish internal inventories regarding products, drug substances, excipients, etc. that are, contain, or make use of nanomaterial(s) or otherwise involve the application of nanotechnology for products regulated by ONADE
- points to consider for technical sections for products containing nanomaterial(s) or otherwise involve the application of nanotechnology that might require additional data or special steps to address potential safety or quality issues
- general considerations for generic investigational new animal drug (JINAD) files and applications

II. WHAT MATERIALS ARE CONSIDERED AS NANOMATERIALS?

The science of nanotechnology is producing novel nanomaterials to be used in drug formulation and drug delivery. Nanomaterials can have chemical, physical and biological properties that differ from those of their non-nanomaterial counterparts.

In July 2007, the FDA Nanotechnology Task Force issued its initial report¹ to conclude that the current regulatory authority over products subject to premarket review (*e.g.* drugs) is adequate. But the report also highlighted the need for FDA to evaluate the adequacy of current testing approaches to assess safety and other relevant characteristics of FDA regulated products that use nanomaterial(s) or otherwise involve the application of nanotechnology. No regulatory definition for nanomaterial has been adopted by FDA, but in draft guidance the agency has indicated that the following should be asked when considering whether an FDA-regulated product contains nanomaterial(s)²:

- Whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm); or
- Whether an engineered material or end product exhibits 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.

ONADE reviewers should apply these considerations when reviewing submissions. The material may be the active drug substance, excipient, drug delivery platform, or any other component of the formulation.

III. EARLY IDENTIFICATION AND INFORMATION COLLECTION

We review drug products that use nanomaterial(s) or otherwise involve the application of nanotechnology under our existing investigational and application processes. The application of nanotechnology may result in product attributes that differ from those of conventionally-manufactured products, and thus may merit further examination. This document is intended to facilitate early identification of these products. Through early identification, we can request and collect relevant information (*e.g.*, nanomaterial characterization tests, toxicity tests) during the review process. However, FDA does not categorically judge all products containing nanomaterials or otherwise involving application of nanotechnology as intrinsically benign or harmful.

Products containing nanomaterials or otherwise involve the application of nanotechnology will usually be identified by either the sponsor/applicant or CVM.

- If the sponsor identifies the product in their request to open an investigational file, the following will occur:

¹ FDA 2007, A Report of the U.S. Food and Drug Administration Nanotechnology Task Force. (<http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForceReport2007/default.htm>)

² FDA 2014, Guidance For Industry: Considering Whether A FDA Regulated Product Involves the Application of Nanotechnology (<http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm>)

- The target animal division (TAD) reviewer should document preliminary characterization(s) of the nanomaterial(s) (e.g. particle size) and a description of the unique role of the particle size/functionality in relation to the final product in the review (see Appendix I), in addition to the information recommended in P&P 1243.4000. If the information is not available in sponsor's submission, the TAD reviewer should contact the sponsor and ask for the information. The information does not need to be sent in as an amendment. The reviewer needs to record the information from the discussion in the review and in the submission report form (Appendix I).
- The TAD reviewer will use the Nanotechnology Submission Report Form (Appendix I) to report the product to CVM's Nanotechnology Working Group (Nanotechnology WG) mailbox. The Nanotechnology WG will use this information to track products, drug substances, excipients, etc. that contain or make use of nanomaterial(s).
- The Nanotechnology WG will work with the project manager to ensure that the (J)INAD or the approved NADA will be marked in STARS as a submission containing nanomaterial(s) or otherwise involve the use of nanotechnology so that technical section review groups know that they are reviewing a nanotechnology-related submission.

Reviewers and project managers will proactively identify products containing nanomaterial(s) or otherwise involve the use of nanotechnology (e.g., in requests to open investigational files, technical sections, etc.) based on the considerations presented in section II and utilizing the list of terms in Appendix 2 of this document.

If the reviewer identifies the proposed product in an application or submission contains nanomaterial(s) or otherwise involve the use of nanotechnology, the reviewer will notify their team leader and the Nanotechnology WG using the form in Appendix 1.

The Nanotechnology WG will work with the project manager to ensure that the (J)INAD or the approved NADA will be marked in STARS as a submission containing nanomaterial(s) or otherwise involve the use of nanotechnology so that technical section review groups know that they are reviewing a nanotechnology submission.

IV. POINTS TO CONSIDER FOR ONADE REVIEW

A. In the investigational phase (J)INAD

1. Target Animal Safety and Human User Safety reviews

These reviews will document:

- if the sponsor has addressed any unique safety concerns related to the use of nanomaterial(s) in the formulation;
- if applicable, a description of how the sponsor has attempted to characterize those hazards;
- any need for additional separate safety studies or the measurement of additional safety parameters in the margin of safety studies, and
- if applicable, human user safety for products containing nanomaterials, including the potential routes of exposure (e.g., aerosolization, transdermal).

Examples of situations that may pose unique safety concerns include, but are not limited to: changes in drug distribution, genotoxicity, particle trapping, entrance into immunoprivileged sites, and particle aggregation.

2. Effectiveness reviews

Currently, we do not anticipate any specific issues related to nanotechnology that would impact the review process for evaluating effectiveness. The TAD reviewer will follow their division's current procedures for evaluating effectiveness.

3. Review of Formulation Bridging Studies

Because nanotechnology may involve differences in functionality and delivery mechanisms, bridging studies to establish safety or effectiveness (i.e., based upon drug concentrations in serum or plasma) will not be useful unless there is good reason to believe that the concentration of dissolved drug in blood reflects the true drug activity. That is, there should be assurance that the blood concentrations are an accurate reflection of active drug concentrations across the various body tissues and sites of action. If the application or submission contains formulation bridging studies, send a consulting review request to the pharmacokinetic (PK) group.

4. Human Food Safety reviews

Human food safety of products intended for use in food producing animals needs to be evaluated in the context of toxicology and residue chemistry. In addition, if the products possess measurable antimicrobial activities, microbial food safety and potential impact on human intestinal flora should be evaluated.

a. Toxicology

Because limited information exists regarding how the physical and chemical properties of nanomaterials may influence safety, our recommendations on toxicology assessment would be on a case-by-case basis. However, the safety standard of reasonable certainty of no harm remains the same. The HFS reviewer will refer the sponsor to the CVM GFI #149, "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing VICH GL33", for general toxicity study recommendations.

b. Residue Chemistry

The HFS reviewer will refer the sponsor to CVM GFI #3, "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals", for a description of the residue chemistry studies to quantitate and characterize the residues in the edible tissues. CVM will work with the sponsor to customize a development plan to characterize the distribution and potential accumulation of nanomaterials in the different edible tissues of food animals and in milk/eggs.

c. Microbial Food Safety

The HFS reviewer will inform the sponsor to address whether the product has any adverse impact on emergence and development of antimicrobial resistance among food-borne pathogens and related commensal bacteria in the intestinal tract of food producing animals being treated with their proposed product. The HFS reviewer will refer the sponsor to CVM GFI #152 "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern".

The HFS reviewer will inform the sponsor to provide an assessment to determine whether a microbiological acceptable daily intake (mADI) is needed for the product that contains nanomaterial(s) or otherwise involves the use of nanotechnology. The HFS reviewer will refer the sponsor to CVM GFI #159 "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI VICH GL36".

5. Chemistry, Manufacturing and Control (CMC) reviews

The CMC reviewer will use the standard components of the Chemistry, Manufacturing and Controls technical section (21 CFR 514.1 or CTD format³)

³ <http://www.ich.org/products/ctd.html>

to review products that contain nanomaterial(s) or otherwise involve the use of nanotechnology. Considerations for finished drug product include:

- Chemical composition of nanomaterial(s) should be clearly defined, including the choice of surfactant, emulsifier, stabilizer, dispersion agent, etc.
- Critical quality attributes, such as particle size distribution, drug loading, surface properties, purity, and/or rate of release, should be identified, characterized and controlled using the appropriate analytical methods and equipments.
- Manufacturing and quality control measures should be in place to ensure the low batch-to-batch variability.
- Appropriate stability indicating tests are used to monitor the shelf-life of the nanomaterial(s) in the formulation, for example, agglomeration, aggregation, and/or interaction with other ingredients of the formulation should be monitored.

6. Environmental Assessment reviews

- Products that contain nanomaterial(s) or otherwise involve the use of nanotechnology will be evaluated using the same risk assessment paradigm for exposure and effects.
- Submission of an Environmental Assessment (EA) or a claim of categorical exclusion will be required (21 CFR 25.15(a)). Nanomaterial(s) may still be eligible for a categorical exclusion under the existing regulations (21 CFR Part 25.33). The environmental reviewer will make sure that sufficient information is included to conclude that extraordinary circumstances do not exist (21 CFR 25.21).
- If the product does not qualify for a categorical exclusion, an adequate EA will have to be submitted by the sponsor. That EA should be consistent with the recommendations in GFI #89, Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) – Phase I VICH GL6, and possibly GFI #166, Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) – Phase II VICH GL38.

B. JINAD

Because of the formulation complexity and unique targets of many nanotechnology-based products, specialized approaches for determining bioequivalence to pioneer products and for analytical testing methods may be needed. Reviewer should consult team leader and collaborate with other appropriate divisions and groups and make decisions on a case-by-case basis.

This consideration also applies to submissions under the traditional ANADA process where no JINAD is submitted.

C. Supplemental NADA/ANADA Applications

Look for any change in a drug substance or excipient of an approved (A)NADA that may involve replacement with a nanosized counterpart in a supplemental application. If the resulting product may be considered a new product for which a new approval is needed (e.g., effectiveness and/or safety need to be re-assessed), consult your team leader.⁴

D. Labeling

Reviewers should evaluate the need for, and appropriateness of, any labeling statements related to nanomaterial(s) or nanotechnology on a case-by-case basis. In general, the use of nanomaterial(s) does not, by itself, trigger the need for special labeling for an ONADE-regulated drug product that contains nanomaterial(s) or otherwise involves the use of nanotechnology. However, there may be cases where additional labeling may need to be considered (e.g. for safe use of the product).

The reviewer needs to inform the sponsor that a new dose or dosing regimen resulting from drug reformulation that contains nanomaterial(s) or otherwise involves the use of nanotechnology should be clearly identified in the labeling to avoid medication errors.

V. REFERENCES

FDA 2007, A Report of the U.S. Food and Drug Administration Nanotechnology Task Force.

FDA 2014, Guidance For Industry: Considering Whether A FDA Regulated Product Involves the Application of Nanotechnology.

Code of Federal Regulations (Title 21)

Part 25 – Environmental Impact Considerations

Part 514 – New Animal Drug Applications

CVM Program Policy and Procedures Manual

1243.4000 – Processing A Request to Open a (J)INAD File

⁴ See Guidance 191 – Changes to Approved NADAs - New NADAs vs. Category II Supplemental NADAs

CVM Guidance for Industry

Guidance 3 – General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals

Guidance 89 – Environmental Impact Assessments (EIA’s) for Veterinary Medicinal Products (VMP’s) – Phase I VICH GL6

Guidance 149 – Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing VICH GL33

Guidance 152 - Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern

Guidance 159 – Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI VICH GL 36

Guidance 166 - Environmental Impact Assessments (EIA’s) for Veterinary Medicinal Products (VMP’s) – Phase II VICH GL38

Guidance 185 - Target Animal Safety for Veterinary Pharmaceutical Products VICH GL43

Guidance 191 – Changes to Approved NADAs - New NADAs vs. Category II Supplemental NADAs.

VI. VERSION HISTORY

August 30, 2011 – Final version

July 22, 2016 – Revisions made to references and updated to current format

APPENDIX I. NANOTECHNOLOGY SUBMISSION REPORT FORM

Please save this form as a Microsoft word document and email it as an attachment to: mailbox for nanotechnology WG. Please use additional pages and/or consult reviewers of other technical sections if needed to complete the form.

Report # (For WG internal use)	
Application and submission number (e.g., I-XXXXXX-P-XXXX)	
Who identified the product as potentially containing nanomaterials? (i.e. Sponsor or CVM)	
Is this a modification of an approved product or another investigational product? If so, what has been modified?	
Please describe the nanomaterials (e.g., poloxamer 188 micelle with emulsified active, particle size 30 -50 nm, or nanocrystal suspension, particle size 130 - 160 nm, etc.)	
Does the new formulation exhibit properties or phenomena (including physical, chemical or biological effects) attributable to dimension(s) within and above the nanoscale range up to one micrometer, including effects via engineering of the constituent? If so, explain.	
Other information worth recording (e.g., INAD or NADA # of a corresponding product w/o nanomaterials)	
Reviewer Name, Date, HFV code	

APPENDIX II. YOU MIGHT HAVE A NANOTECHNOLOGY PRODUCT IF YOU SEE

A. Any Of These Terms In The Submission⁵

Micelle
Liposome
Dendrimer
Carbon nanotube (CNT)
Polymer
Quantum dot
Nanocrystal
Fullerene
Cyclodextrins

B. Or any reference to:

Self-assembling
Encapsulation
Emulsification
Pegylation
Colloidal
Micronized
Drug delivery or carrier system
Changing a compound's solubility
Long shelf life
Novel and unexplained antimicrobial properties
Increased effectiveness
Reduced dose
Radiographic contrast agents
Flamel Technologies Medusa[®] Platform

⁵ This list provides examples and is not meant to be exhaustive.