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

I. PURPOSE

This document provides:

- points to consider in identifying new animal drug products containing nanomaterials or involving the application of nanotechnology
- a means to collect information and establish internal inventories regarding new animal drug 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 new animal drug 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 investigational new animal drug (INAD) and generic investigational new animal drug (JINAD) files and new animal drug applications (NADA) and abbreviated new animal drug (generic) applications (ANADA)

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 report to conclude that the current regulatory authority over products subject to premarket review (e.g. drugs) is adequate.[1] 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

[1] FDA 2007, A Report of the U.S. Food and Drug Administration Nanotechnology Task Force. (https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-task-force-report-2007)

has been adopted by FDA, but in the 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 new animal 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 new animal drug 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.

New animal drug 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 new animal drug product in their request to open an investigational file as containing nanotechnology or involving application of nanotechnology, the following will occur:
    - 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.
    - The TAD reviewer will use the Nanotechnology Submission Report Form to report the new animal drug product to CVM's Nanotechnology

[2] FDA 2014, Guidance For Industry: Considering Whether a FDA Regulated Product Involves the Application of Nanotechnology https://www.fda.gov/media/88423/download

Working Group (Nanotechnology WG) mailbox.[3,4] 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 and the Document Control Unit (DCU) to ensure that the (J)INAD or the approved (A)NADA will be marked in our Submission Tracking and Reporting System (STARS) as NANOTECH, indicating that the application contains nanomaterial(s) or otherwise involve the use of nanotechnology . This designation will appear on the Document Overview Page of STARS.

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Document Classification is a searchable criterion. Reviewers are able to recover all the documents in STARS that are designated as NANOTECH using Document Search.

[3] The Nanotechnology Submission Report Form is on the ONADE Forms Page in SharePoint: Internal information redacted

[4] Internal information redacted

Internal information redacted

Reviewers and project managers will proactively identify new animal drug 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 of this document. If the reviewer identifies the proposed new animal drug 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 by using the Nanotechnology Submission Report Form. Nanotechnology WG will follow the same procedure as outlined above to mark the document as NANOTECH in STARS.

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 new animal drug 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 new animal drug products intended for use in food producing animals needs to be evaluated in the context of toxicology and residue chemistry. In addition, if the new animal drug 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 and honey.

c. Microbial Food Safety

The HFS reviewer will inform the sponsor to address whether the new animal drug 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 new animal drug 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 new animal drug 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 Common Technical Document (CTD) format) to review new animal drug products that contain nanomaterial(s) or otherwise involve the use of nanotechnology.[5] CMC Reviewers are encouraged to consult CDER/CBER's Draft Guidance for Industry "Drug Products, Including Biological Products, that Contain Nanomaterials"[6] as needed. Considerations for finished new animal drug product include:

- Chemical composition of nanomaterial(s) should be clearly defined, including the choice of surfactant, emulsifier, stabilizer, dispersion agent, etc.

[5] http://www.ich.org/products/ctd.html
[6] FDA Draft Guidance for Industry: Drug Products, Including Biological Products, that Contain Nanomaterials https://www.fda.gov/media/109910/download

- 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 equipment.

- 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

   - New animal drug 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 new animal drug 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 new animal drug products, specialized approaches for determining bioequivalence to the reference listed new animal drug 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 NADAs and ANADAs

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 anew approval (i.e., new original application) is needed (e.g., effectiveness and/or safety need to be re-assessed), consult your team leader.[7]

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

Guidance for Industry

CVM Guidance 3 – General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food-Producing Animals

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

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

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

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

[7] See Guidance 191 – Changes to Approved NADAs - New NADAs vs. Category II Supplemental NADAs

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

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

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

FDA 2017 Guidance for Industry: Drug Products, Including Biological Products, that Contain Nanomaterials

FDA 2019 Draft Guidance for Industry: Drug Products, Including Biological Products, that Contain Nanomaterials

CVM Program Policies and Procedure Manual – ONADE Reviewer's Chapter

1243.4000 Processing a Request to Open an Investigational (INAD) or Generic Investigational New Animal Drug (JINAD) File

VI. VERSION HISTORY

August 30, 2011 – Final version

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

July 18, 2019 – Updated to fix broken urls that were broke when FDA migrated to a new website. Added a new reference footnote 5 under section IV.A.5 and section V. Added CVM Nanotechnology WG's email address under section III.

September 25, 2020 – An interactive form for reporting was created from the information formerly in Appendix I. Therefore, that appendix was removed from this document. Updated to include two screen shots of STARS to show how the document is identified as NANOTECH in STARS after the reporting and how to do a document search for NANOTECH documents.

January 27, 2022 – Quality system review conducted of the document and no updates or revisions were necessary at this time.

APPENDIX: YOU MIGHT HAVE A NANOTECHNOLOGY PRODUCT IF YOU SEE

A. Any of These Terms in the Submission[8]

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

[8] This list provides examples and is not meant to be exhaustive.