OFFICE OF PHARMACEUTICAL SCIENCE

Reporting Format for Nanotechnology-Related Information in CMC Review

CONTENTS

PURPOSE

- This MAPP provides chemistry, manufacturing, and controls (CMC) reviewers within the Office of Pharmaceutical Science (OPS) with the framework by which relevant information about nanomaterial-containing drugs will now be captured in CMC reviews of current and future CDER drug application submissions. This information will be entered into a nanotechnology database under construction and ultimately be used to develop policy regarding these products.

BACKGROUND

- Because development of nanotechnology-based drugs is still in its infancy, there are no established standards for the study or regulatory evaluation of these products. In response to this, the Food and Drug Administration (FDA) established the Nanotechnology Task Force, which issued a report in July 2007. This report included a series of recommendations on scientific and regulatory policy issues. Some of the recommendations highlighted the need for Center-specific guidance documents to help support the development of safe and effective nanomaterial-containing products. However, in order to develop guidance for industry, CDER needs to organize all the data submitted in support of nanotechnology-based drug applications.

- To that end, CDER's Office of Pharmaceutical Science (OPS), Science and Research Staff, started to develop a comprehensive database of products containing nanomaterials that were the subject of CDER drug applications. In developing this database, it became clear early on that much of the information that was necessary to populate the fields of the database was not being captured consistently in CMC reviews. CDER needed to establish appropriate procedures by which to effectively and efficiently track applications for products that contain nanomaterials. Consequently, CDER found it important to develop a format to help reviewers document in their reviews relevant information when an application is for a product containing nanomaterials.

REFERENCES

- MAPP 6030.1, IND Process and Review Procedures (Including Clinical Holds).
- Document Archiving, Reporting, and Regulatory Tracking System (DARRTS).
- Division File System (DFS).
- Nanotechnology: A Report of the U.S. Food and Drug Administration Nanotechnology Task Force.

DEFINITIONS[1]

- **Nanomaterial/Nanoscale Material:** Any materials with at least one dimension smaller than 1,000 nm.
- **Nanomedicine:** The use of nanoscale materials for medical applications.
- **Characterization:** Physicochemical evaluation of relevant drug properties.

RESPONSIBILITIES

- OPS CMC reviewers are responsible for adequately and correctly documenting nanotechnology-related information in their reviews of CDER drug application submissions. This information is to appear in reviews in the form of a table (see Attachment A). The purpose of employing this table is to allow for nanotechnology-related information to be presented in a standardized and searchable format.
- Secondary CMC reviewers, as well as OPS management, are responsible for ensuring that CMC reviews document in the table whether the application contains nanotechnology-related information and that the information is accurate.
- Initially, OPS's Science and Research Staff will be responsible for conducting the DARRTS/DFS searches so they can populate the nanotechnology database. Who will be responsible for maintaining the database on a permanent basis will be determined once the database is in place.

PROCEDURES

- To populate the nanotechnology database, OPS's Science and Research Staff will search CMC reviews in DARRTS/DFS using established terms (see Attachment B). If, in a CMC review for a particular drug application, the response to question 2 in the table provided in Attachment A is "Yes" (meaning that the application contains

[1] The definitions described in this section apply only to this MAPP. See Attachment B for a list of search terms that CDER is using to populate the nanotechnology database. CMC reviewers can refer to this list to identify nanomaterials in drug products.

nanomaterials), then that review will be selected and all the relevant nanotechnology-related information in that CMC review will be gathered.

- Accordingly, that information will be entered into the CDER nanotechnology drug product database. The database entry template is provided in Attachment C.

- Below is a list of the information that a CMC reviewer should document (if available) in the appropriate CMC review to allow for a better understanding of the properties of nanomaterials. (See the nanotechnology product review flow chart in Attachment D for an illustrated version of what is listed below.)

  - Whether the application contains nanomaterials.[2]

  - What type of nanomaterial is included in the product (examples of this are listed as search terms in Attachment B).

  - Whether the nanomaterial is a reformulation of a previously approved product.

  - Whether the nanomaterial is part of the drug substance (active pharmaceutical ingredient (API)) or the drug product (carrier, excipient, or packaging).

  - Whether the particle size was described in the application and what the reported particle size (average primary particle size, size range distribution, aggregation status, agglomeration status) is. With changes in formulation, it is possible that the information on particle size may change. If that is the case, the change in particle size will have to be reflected in the nanotechnology section of any subsequent review so that the most up-to-date information is available in the database.

  - Whether the techniques used to assess particle size are thoroughly described with respect to their adequacy. Attachment E provides examples of techniques that may be used to assess size, as well as examples of techniques that may be used to evaluate other nanomaterial properties. Reviewers can use their scientific judgment to determine the adequacy of the techniques used by the sponsor.

  - Whether the nanomaterial is soluble or insoluble in an aqueous environment (e.g., gold nanoparticle (insoluble) versus nanocrystal (soluble)).

  - What other properties of the nanomaterial (e.g., surface charge, surface properties) were measured and reported in the application and how those properties were measured (e.g., surface probe microscopy, laser Doppler

[2] This element must be documented.

electrophoresis). Attachment E provides a list of possible properties and methodologies that could be used to measure them.

- CMC reviewers will copy, paste, and fill in Attachment A for the CMC review in section "P.2.2.3 Physicochemical and Biological Properties (ICH-CTD-MQ4)." By placing this table in the same section of all CMC reviews, the CMC reviewers will ensure consistency and allow for more efficient searching of the reviews. Each new CMC review must contain the most up-to-date populated version of the table provided in Attachment A. If new information is not added, this must be indicated under question 1 in the table.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

Attachment A: Nanotechnology Product Evaluating Questions

1) This review contains new information added to the table below: _____Yes _____No Review date: _____
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes_____; No_____ ; Maybe (please specify)_____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____ 3 b) What is the source of the nanomaterial?_____
4) Is the nanomaterial a reformulation of a previously approved product? Yes_____ No_____
5) What is the nanomaterial functionality? Carrier_____; Excipient_____; Packaging_____; API_____; Other_____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment? Soluble _____; Insoluble_____
7) Was particle size or size range of the nanomaterial included in the application? Yes_____ (Complete 8) ; No_____(Go to 9)
8) What is the reported particle size? Mean particle size_____ ; Size distribution_____; Other_____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10) What other properties of the nanomaterial were reported in the application (see Attachment E)? _____
11) List all methods used to characterize the nanomaterial. _____

Attachment B: Search Terms for Populating the CDER Nanotechnology Drug Product Database

- **Nanotechnology:** The understanding and control of matter at dimensions between approximately 1 to 100 nanometers, where unique phenomena enable novel applications. (*Source:* National Nanotechnology Initiative Definition)

- **Nanoparticle:** Nano-object with all three external dimensions at the nanoscale that is the size range from approximately 1 nm to 100 nm. (*Source:* www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=44278; last accessed December 2008) Polymeric nanoparticle platforms are characterized by their physicochemical structures including solid nanoparticles, nanoshell, dendrimer, polymeric micelle, and polymer-drug conjugates. (*Source:* F. Alexis, et al., Factors affecting the clearance and biodistribution of polymeric nanoparticles, Mol Pharm., 2008)

- **Dendrimer:** A polymer in which the atoms are arranged in many branches and subbranches along a central backbone of carbon atoms. (*Source:* American Heritage Science Dictionary)

- **Liposomes:** Vesicles composed of one or more bilayers of amphiphatic lipid molecules enclosing one or more aqueous compartments. (*Source: Guidance for Industry: Liposome Drug Products*, August 2002; last accessed May 2008)

- **Micelles:** Self-assembling nanosized colloidal particles with a hydrophobic core and hydrophilic shell currently used for the solubilization of various poorly soluble pharmaceuticals. (*Source:* V.P. Torchilin, Lipid-core micelles for targeted drug delivery, Curr Drug Deliv., 2005)

- **Nanoemulsions:** Emulsions with droplet size in the nanometer scale. Emulsion is a thermodynamically unstable system consisting of at least two immiscible liquid phases, one of which is dispersed as globules (the dispersed phase), in the other liquid phase (the continued phase), stabilized by the presence of an emulsifying agent. However, one type of emulsion—microemulsions—does demonstrate stability. (*Source:* Chapter 18: Coarse Dispersions, In A. Martin (ed.), Physical Pharmacy: physical chemical principles in the pharmaceutical sciences, 1993)

- **Nanocrystal:** Nanoscale solid formed with a periodic lattice of atoms, ions, or molecules. (*Source:* www.bsi-global.com)

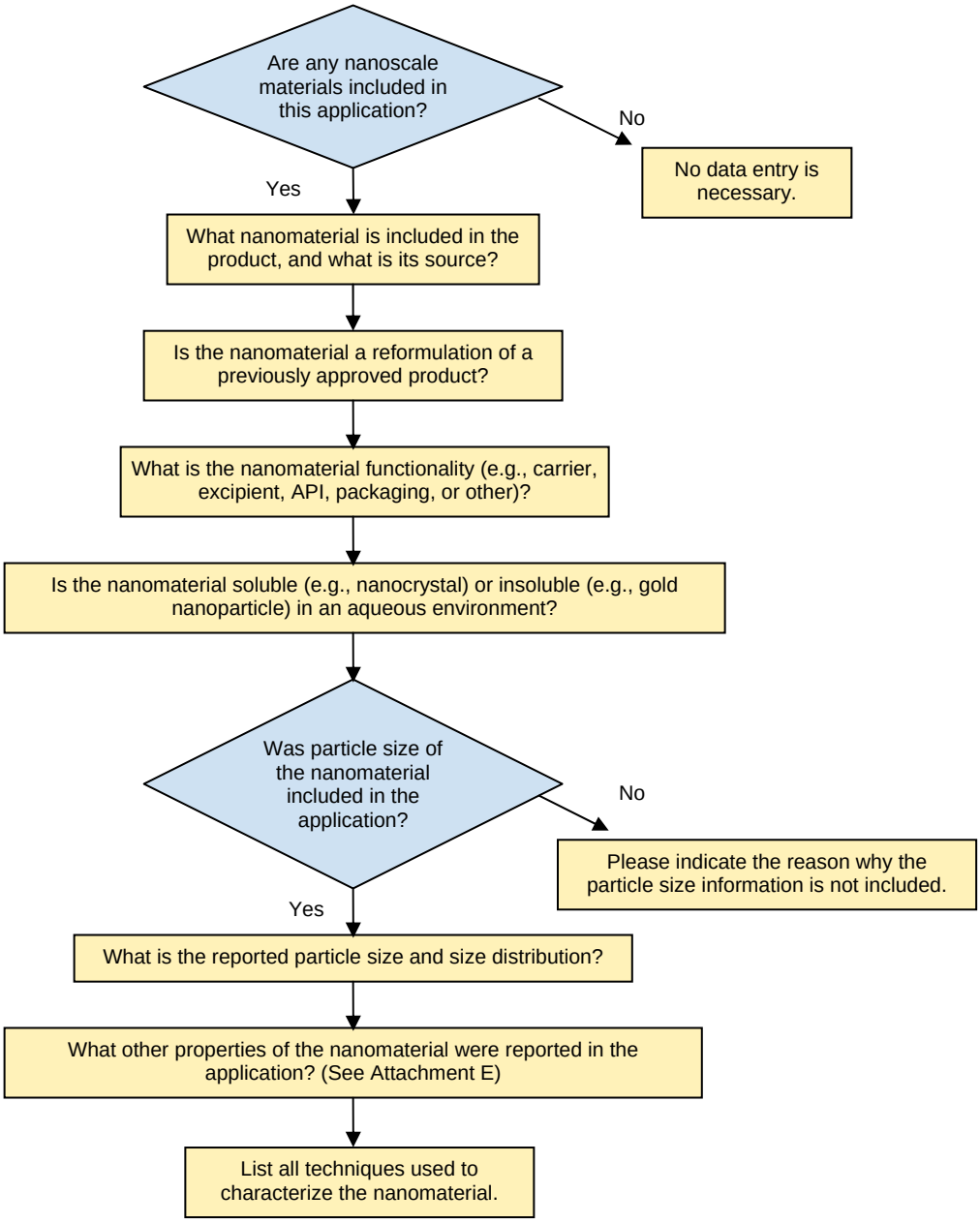
- **Primary Particle:** Smallest identifiable subdivision in a particulate system. (*Source:* www.bsi-global.com)

- **Metal Colloids:** Metal nanoparticles in colloidal systems where the term colloidal refers to a state of subdivision. This implies that the molecules or polymolecular particles are dispersed in a medium and have at least in one direction a dimension roughly between 1 nm and 1µm or, in a system, have discontinuities at distances of that order. For example, silver, gold, titanium dioxide, zinc oxide, and iron oxide. (*Source:* International Union of Pure and Applied Chemistry, Manual of Symbols and Terminology for Physicochemical Quantities and Units, 2001)

Attachment C: Template for CDER Nanotechnology Drug Product Database Entry

Comment	For any comments or QC for the data entered
ID	Database entry #
NDA/IND	NDA # and related IND #
Drug Name	Name of drug (Trade name; generic name; code name)
Description	Description of drug substance or drug product that involves nanotechnology, e.g., the drug is encapsulated within liposomes, dendrimer, or PEGylated nanoparticle, etc.
Indication	Indication of the drug, e.g., antiemetic, antineoplastic, etc.
Route of Admin	Oral, I.V., etc.
Sponsor	Name of Sponsor
Approval Date	FDA approval date
Responsible Division	Name of responsible division and HFD code
Particle Size Range	Mean particle size and particle size distribution
Technique for Assessing	Characterization technique for assessing nanospecific properties. Refer to Attachment E from the MAPP.
Search Keys	Keywords that are used to search to find nanomaterial from database, e.g., nanoparticle. Refer to Attachment B from the MAPP.
Link to Quality Reviews	Create a link to the Chemistry Reviews
Link to Clinical Reviews	Create a link to the Clinical Reviews
Link to ClinPharm Reviews	Create a link to the ClinPharm Reviews
Link to PharmTox Reviews	Create a link to the PharmTox Reviews

Attachment D: Nanotechnology Product Review Flow Chart



Attachment E: Common Techniques Used to Characterize Nanomaterials

PROPERTIES[a]	**COMMON TECHNIQUES**[b,c]
MORPHOLOGY	
Size (primary particle)	TEM, SEM, AFM, XRD
Size (primary/aggregate/agglomerate)[d]	TEM, SEM, AFM, DLS, FFF, AUC, CHDF, XDC, HPLC, DMA(1)
Size distribution	TEM, SEM, AFM, DLS, AUC, FFF, HPLC, SMA
Molecular weight	SLS, AUC, GPC
Structure/Shape	TEM, SEM, AFM, NMR
Stability (3D structure)	DLS, AUC, FFF, SEM, TEM
SURFACE	
Surface area	BET
Surface charge	SPM, GE, Titration methods
Zeta potential	LDE, ESA, PALS
Surface coating composition	SPM, XPS, MS, RS, FTIR, NMR
Surface coating coverage	AFM, AUC, TGA
Surface reactivity	Varies with nanomaterial
Surface-core interaction	SPM, RS, ITC, AUC, GE
Topology	SEM, SPM, MS
CHEMICAL	
Chemical composition (core, surface)	XPS, MS, AAS, ICP-MS, RS, FTIR, NMR
Purity	ICP-MS, AAS, AUC, HPLC, DSC
Stability (chemical)	MS, HPLC, RS, FTIR
Solubility (chemical)	Varies with nanomaterial
Structure (chemical)	NMR, XRD
Crystallinity	XRD, DSC
Catalytic activity	Varies with nanomaterial
OTHER	
Drug loading	MS, HPLC, UV-Vis, varies with nanomaterial
Drug potency/functionality	Varies with nanomaterial
In vitro release (detection)	UV-Vis, MS, HPLC, varies with nanomaterial
Deformability	AFM, DMA(2)

[a] *The property list is not definitive. Other properties may be reported.*

[b] *Only common techniques are listed. Other techniques may be valid. The choice of techniques should be justified.*

[c] *An abbreviation list and references are provided on the following page.*

[d] *These techniques will measure the average particle size, but can not necessarily distinguish between primary particles, aggregates, and agglomerates.*

ABBREVIATIONS

AAS	Atomic absorption spectroscopy	ITC	Isothermal titration calorimetry
AFM	Atomic force microscopy	LDE	Laser doppler electrophoresis
AUC	Analytical ultracentrifugation	MS	Mass spectrometry (GCMS, TOFMS, SIMS, etc.)
BET	Brunauer, Emmett, and Teller method	NMR	Nuclear magnetic resonance
CHDF	Capillary hydrodynamic fractionation	PALS	Phase analysis light scattering
DLS	Dynamic light scattering	RS	Raman spectroscopy
DMA(1)	Differential mobility analyzer	SEM	Scanning electron microscopy
DMA(2)	Dynamic mechanical analyzer	SLS	Static light scattering
DSC	Differential scanning calorimetry	SMA	Scanning mobility particle sizer
ESA	Electroacoustic spectroscopy	SPM	Surface probe microscopy (AFM, STM, NSOM, etc.)
FFF	Field flow fractionation	TEM	Transmission electron microscopy
FTIR	Fourier transform infrared spectroscopy	TGA	Thermal gravimetric analysis
GE	Gel electrophoresis	UV-Vis	Ultraviolet-visible spectrometry
GPC	Gel permeation chromatography	XDC	X-ray disk centrifuge
HPLC	High performance liquid chromatography	XPS	X-ray photoelectron spectroscopy
ICP-MS	Inductively coupled plasma mass spectrometry	XRD	X-ray diffraction

References

Tyner, K.M. “Nano-methods” in *Handbook of Analysis and Pharmaceutical Quality* , Shayne Gad, Ed. John Wiley and Sons, NJ. *In publication.*

Dair, B.J., Tyner, K.M., Sapsford, K.E. “Techniques for the characterization of nanoparticle-bioconjugates” in *Nanoparticles in Bioengineering* , Raushal Rege and Igor Medintz, Ed. Artech House, MA. *In publication.*