

Regulatory Hurdles for Nanotechnology

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Current state of affairs

- n Regulatory authority for food additives is not expected to be altered to address nanoscale particles.
- n Questions that regulators need to ask include:
 - l What are the appropriate criteria for defining their specifications of identity and purity for determining safety?
 - l What types of toxicity testing protocols are appropriate for establishing safe conditions of use?
 - l Do existing authorizations cover these products?



Guidance for Approval of Food Additives and Food Contact Substances

n Currently Available

- | Chemistry Guidance for Color Petitions (July 2009)
- | Chemistry Guidance for Direct Food Additive Petitions (March 2009)
- | Chemistry Guidance for Food Contact Notifications (December 2007)



Chemistry Guidance for Food Additive Petitions

Section III.A. Identity:

“...If the particle size is important for the additive to achieve its intended technical effect, such that the additive is produced or processed using techniques or tools that manipulate the particle size and may contain altered particles that are formed as manufacturing by-products, data on the size (average and distribution), shape, surface area (average and distribution), surface charge (zeta potential), and morphology of the particles, as well as any other size-dependent properties (e.g., agglomeration, aggregation, dispersion) should be included, as appropriate.”



Chemistry Guidance for Food Additive Petitions

Section III.C. Specifications for Identity and Purity:

“...Parameters related to the particle size, shape, and surface properties of the food additive, as appropriate, if particle size is important for the identity and functionality of the additive.”

Section III.E. Intended Technical Effect and Use:

"...A clear statement of the intended technical effect(s) of the additive in food. If technical effect of the additive is related to particle size, the statement should explain how size-dependent properties of the additive affect functionality (e.g., solubility, viscosity, stability, antibacterial properties, antioxidant properties)."



Chemistry Guidance for Food Contact Notifications

Section II.A.5. Physical/Chemical Specifications:

"...In cases where particle size is important to achieving the technical effect or may relate to toxicity, sponsors should describe particle size, size distribution, and morphology, as well as any size-dependent properties."

Section II.C. Technical Effect:

"...If technical effect is dependent on particle size, sponsors should present data that demonstrate the specific properties of the particles that make them useful for food-contact applications."



Under Consideration for Revision

- n Toxicology Guidance for Food Contact Notifications
- n Toxicology Guidance for Direct Food Additives
- n Guidance for GRAS Substances

*Contact FDA for specific guidance in the interim



Impact on Regulatory Status

- 1- The majority of food additive regulations do not include size-dependent specifications such as particle size, size distribution and morphology.
- 2- Under section 402 of the Act, it is the responsibility of both the manufacturer and the end user of the food ingredient or food contact substance to ensure that the use of the food ingredient or food contact substance is safe and lawful.



Impact on Regulatory Status

- 3- Safety of nanoscale versions of compounds can not be demonstrated solely on evidence from conventional scale counterparts due to novel properties and physical characteristics of nanoscale material.

As a result of these three factors, the regulatory status of nanoscale versions of compounds is frequently questioned.



Guidance for Authorized Products

Industry has requested that FDA prepare guidance that clarifies when nanoscale versions of approved food additives are covered by the existing regulations.

FDA is in the process of drafting a guidance document that will address all manufacturing changes including nanotechnology.

FDA hopes to have a draft ready for publication in 2010.



Manufacturing Changes

- n Manufacturing changes, especially nanotechnology, have the potential to substantially alter the identity or toxicity of a compound.
- n Manufacturers may need to re-evaluate the safety of the modified product before it is used.
- n This evaluation may be informal.



Area of Consideration: Impact on Identity

- n Does the manufacturing change alter:
 - | Identity (chemical composition, physical and chemical properties, function, incidental byproducts)
 - | Purity
 - | Intended Physical or Technical Effects
- n Is the modified product:
 - | In compliance with existing specifications or limitations
 - | Produced and used under good manufacturing practices



Area of Consideration: Impact on Safety

- n Is the uptake, absorption and bioavailability of the modified product different than the conventional product?
- n Are new impurities detected at concentrations that are of concern?
- n Are there new toxicology issues that were not previously addressed?



Approved Direct or Indirect Food Additives

The use of the chemical is no longer in compliance with an existing regulation if the change in manufacturing practices alters the chemical such that:

- the **chemical identity** and **composition** are no longer the same as the approved compound,
- the **use or intended use** is no longer in conformity with the regulation,
- the additive is no longer produced under **good manufacturing practices**, or
- the **quantity of the additive** in food renders it injurious to health.



Analysis currently being done on case by case basis.



Food Contact Notifications

Under Section 409 (h)(2)(C) of the Act, a food contact substance approval does not apply to a similar or identical substance manufactured or prepared by a person other than the manufacturer identified in the notification.

Any manufacturing change intended to produce nanoscale particles would be considered a significant change, if such particles were not part of the original FCN.

Significant manufacturing changes resulting in substantive changes in the food contact substance require a new FCN.



Threshold of Regulation

- n Any significant change in manufacturing may result in a food additive or food contact substance that is not covered by an existing TOR exemption.
- n New technologies may raise new safety issues.
- n An abbreviated review, such as TOR, would generally not be considered suitable in these situations.



Generally Recognized as Safe

Generally Recognized as Safe designation is for the use of substances whose safe conditions of use are well established and well recognized among qualified scientists.



Generally Recognized as Safe

Greater uncertainties in regard to toxicity of nanoscale versions of otherwise GRAS substances may preclude a GRAS determination unless there is sufficient toxicity information on the nanoscale version of the compound.



Conclusions

FDA advises manufacturers to seek premarket clearance for nanomaterials intended for use in food or food packaging.



Further Information Sources

Useful Websites

Food and color additives program:

<http://www.fda.gov/Food/FoodIngredientsPackaging/FoodAdditives/default.htm>

GRAS Notification Program:

<http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/default.htm>

Guidance and reference documents for petitions and notifications:

<http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/default.htm>

FDA has recently moved many of its web pages.

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