Contains Nonbinding Recommendations
Draft-Not for Implementation

Lead in Cosmetic Lip Products and Externally Applied Cosmetics: Recommended Maximum Level Guidance for Industry

Draft Guidance

This guidance is being distributed for comment purposes only.

Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact the Center for Food Safety and Applied Nutrition (CFSAN) at 240-402-1130.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition

December 2016

Contains Nonbinding Recommendations

Draft-Not for Implementation

Table of Contents

Contains Nonbinding Recommendations

Draft-Not for Implementation

Lead in Cosmetic Lip Products and Externally Applied Cosmetics: Recommended Maximum Level[1] Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration's (FDA or we) on this topic. It does not establish 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

This guidance provides a recommended maximum level of 10 parts per million (ppm) for lead as an impurity in cosmetic lip products and externally applied cosmetics that are marketed in the United States. FDA (or "we") has concluded that a recommended maximum level of 10 ppm for lead as an impurity in cosmetic lip products and externally applied cosmetics would not pose a health risk. We consider the recommended maximum lead level to be achievable with the use of good manufacturing practices and to be consistent with the 10 ppm maximum lead level for similar products recommended by other countries. For additional discussion of the scientific and legal background and rationale underlying this recommended level, see "Supporting Document for Recommended Maximum Lead Level in Cosmetic Lip Products and Externally Applied Cosmetics" (http://www.fda.gov/Cosmetics/GuidanceRegulation/GuidanceDocuments/ucm517327.htm).

The issuance of this guidance supports our effort to limit human exposure to lead in finished FDA-regulated cosmetic products by educating new manufacturers who wish to enter the market and encouraging current manufacturers to continue to follow or improve on voluntary good manufacturing practices that limit trace amounts of lead as an impurity. This guidance applies to cosmetic lip products (such as lipsticks, lip glosses, and lip liners) and externally applied cosmetics (such as eye shadows, blushes, shampoos, and body lotions) marketed in the United States.[2] This guidance does not apply to topically applied products that are classified as drugs or to hair dyes that contain lead acetate as an ingredient.

[1] This guidance has been prepared by the Office of Cosmetics and Colors in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

[2] Cosmetic lip products are applied to the mucous membrane and therefore are not considered externally applied cosmetics (See 21 CFR 70.3(v)).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe our 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 FDA guidances means that something is suggested or recommended, but not required.

II. Background

We regulate cosmetics under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and Fair Packaging and Labeling Act (FPLA). These laws require that cosmetics marketed in the United States be safe under their intended and customary conditions of use, and be properly labeled. Cosmetics are not subject to pre-market approval by FDA. However, pre-market approval is required for the color additives used as ingredients in cosmetics.

Although we have not set limits for lead as an impurity in cosmetics, most listed color additives have specifications for lead as an impurity as part of our requirements for their safe use. This guidance supports our effort to limit human exposure to lead in finished products by recommending a maximum level of 10 ppm lead as an impurity in cosmetic lip products and externally applied cosmetics.

The International Cooperation on Cosmetics Regulation and regions such as Canada and the European Union have set a limit of 10 ppm for lead as an impurity in cosmetics based on considerations of a reasonably achievable level, scientific risk assessment, good manufacturing practices, technical feasibility, and appropriate analytical methods (Refs. 1, 2). This guidance is consistent with those efforts.

III. Discussion

A. Recommended Maximum Lead Level in Cosmetic Lip Products and Externally Applied Cosmetics

Between 2007 and 2009, FDA scientists developed and validated a total dissolution method for analyzing lead in lipstick and used this method to determine the lead content in a selection of 20 commercially available lipsticks on the U.S. market (Ref. 3). In 2010, using the same analytical method, we obtained results for lead content in 400 lipsticks and other cosmetic lip products available in the U.S., and in 2012, obtained similar results for an additional 30 cosmetic lip products (Refs. 4, 5, 6, 7). Finally, between 2012 and 2013, we used a more common extraction method for determining lead in an additional 29 cosmetic lip products (Ref. 7). The lead levels found in our surveys ranged from 0.026 ppm (the detection limit of the total dissolution method for the studies) to a maximum of 7.19 ppm in one lipstick. The average lead concentration was 1.09 ppm.

Between 2011 and 2012, we used a total dissolution method to obtain results for lead content in 120 externally applied cosmetic products available on the U.S. market, which included eye shadows, blushes, body lotions, mascaras, foundations, body powders, compact powders,

shaving creams, and face paints (Refs. 6, 7). Between 2012 and 2013, we used the extraction method for determining lead in an additional 86 externally applied cosmetics (Ref. 7). The lead levels found in our surveys ranged from 0.0084 ppm (the detection limit of the total dissolution method for these studies) to a maximum of 14 ppm in one eye shadow and one blush. The average lead concentration ranged from below the detection limit in shaving creams to 4.6 ppm in compact powders.

These surveys indicate that levels of lead in the cosmetic lip products and externally applied cosmetics we have sampled are for the most part well below 10 ppm, leading us to expect that this recommended maximum level is achievable by all manufacturers of these products. However, in our surveys, which do not necessarily reflect the full range of products that are currently on the market, a small number of samples had lead levels that exceed the maximum level we are recommending. Our goal is to ensure that cosmetic lip products and externally applied cosmetics do not contain lead as an impurity at levels that would pose a health risk. We have determined that a maximum level of 10 ppm in cosmetic lip products and externally applied cosmetics would not pose a health risk, but we encourage manufacturers of these products to follow or continue to follow manufacturing practices that allow them to achieve levels of lead lower than 10 ppm whenever feasible.

We have concluded that a maximum level of 10 ppm for lead as an impurity in cosmetic lip products and externally applied cosmetics should be readily achievable by manufacturers that source their ingredients appropriately and use good manufacturing practices. Modern analytical capability permits determination of lead at ppm levels, thus enabling manufacturers to avoid the purchase of ingredients with unacceptably high levels of lead and to determine whether lead is introduced into their products during the manufacturing process.

B. Exposure Assessment and Public Health Impact of Recommended Maximum Lead Level in Cosmetic Lip Products and Externally Applied Cosmetics

As explained in more detail in our supporting document, the routes of exposure to lead from cosmetic lip products are incidental ingestion and dermal absorption and the route of exposure to lead from externally applied cosmetics is dermal absorption. To assess the exposure to lead from cosmetic lip products and externally applied cosmetic products, we assumed these products contain 10 ppm lead because, as noted above, that impurity level should be readily achievable by manufacturers. Additionally, 10 ppm lead is consistent with the 10 ppm maximum lead level for similar products recommended by the International Cooperation on Cosmetics Regulation and regions such as Canada and the European Union.

1. Exposure to Lead from Cosmetic Lip Products

The composition of cosmetic lip products limits the ability for lead present as an impurity to diffuse from a product and be absorbed by the skin. Therefore, dermal absorption of lead from cosmetic lip products is negligible, and we have concluded that systemic exposure to lead from these products is primarily by incidental ingestion.

We used an approach previously employed by FDA for estimating exposure to lead from food to estimate exposure to lead from cosmetic lip products (Ref. 8). We estimated that maximum exposure to 10 ppm lead from a cosmetic lip product is 0.24 µg/day for adults and adolescents age 13 years or older and 0.024 µg/day for children age 12 years or younger (assuming that children age 12 years or younger use 10% as much of these products as adults) (Ref. 9). We determined that the potential elevation of blood lead levels from 10 ppm lead in these products is too small to be measured in routine blood analysis and requires state of the art analytical technology (Ref. 10).

2. Exposure to Lead from Externally Applied Cosmetics

Dermal absorption of lead from externally applied cosmetics is very small. Results for lead uptake by the skin were reported for four lead compounds that resemble cosmetic ingredients (Ref. 11). Based on those data, we estimated that only a very small amount (0.41%) of the lead present as an impurity in an externally applied cosmetic is absorbed by the skin.

The amount of exposure to lead as an impurity in externally applied cosmetics depends on whether the product is a "leave-on" product (such as eye shadow or body lotion) or a "rinse-off" product (such as shampoo or shaving cream). The amount of exposure also depends on how much product is applied to the skin. For example, eye shadows are applied in very small amounts (40 mg/day) and only around the eyes (Ref. 12). Because dermal absorption of lead is so small, we estimated that exposure to 10 ppm lead from an eye shadow is only 1.64×10^{-3} µg/day for adults and adolescents age 13 years or older and 1.64×10^{-4} µg/day for children age 12 years or younger (assuming that children age 12 years or younger use 10% as much eye shadow as adults). This means that exposure to lead from an eye shadow is approximately 150 times lower than exposure to lead from a cosmetic lip product.

The amount of exposure to lead as an impurity in a product such as body lotion is higher because average applications are higher (8.7 g/day) (Ref. 9). Based on body surface area calculations from reported height and weight data, we estimated that children age 6-18 use 65% as much body lotion as adults age ≥19 and children age 1-5 use 34% as much body lotion as adults age ≥19 (Refs. 10, 13). We then estimated that exposure to 10 ppm lead from a body lotion is 0.36 µg/day for adults age ≥19, 0.23 µg/day for children age 6-18, and 0.12 µg/day for children age 1-5. In addition, our surveys found that body lotions actually contain very little lead (0.04 to 0.10 µg/g) (Refs. 6, 7). Therefore, we estimated that exposure to lead from a body lotion containing 0.10 µg/g (0.10 ppm) lead is 0.0036 µg/day for adults age ≥19, 0.0023 µg/day for children age 6-18, and 0.0012 µg/day for children age 1-5, or 67 times lower for adults and up to 20 times lower for children than exposure to lead from a cosmetic lip product.

Exposure to lead from externally applied cosmetics is up to 150 times lower than exposure to lead from cosmetic lip products. Therefore, the potential elevation of blood lead levels from 10 ppm lead in these products is too small to be measured in routine blood analysis and requires state of the art analytical technology (Ref. 10).

3. Public Health Impact of Recommended Maximum Lead Level in Cosmetic Lip Products and Externally Applied Cosmetics

Based on our exposure assessment, we have concluded that a recommended maximum level of 10 ppm for lead as an impurity in cosmetic lip products and externally applied cosmetics would not pose a health risk. The issuance of this guidance supports our effort to limit human exposure to lead in finished FDA-regulated cosmetic products by educating new manufacturers who wish to enter the market and encouraging current manufacturers to continue to follow or improve on voluntary good manufacturing practices that limit trace amounts of lead as an impurity. We consider the recommended maximum lead level to be achievable with the use of good manufacturing practices and to be consistent with the 10 ppm maximum lead level for similar products recommended by other countries.

Lead is a chemical element for which toxicity in humans has been well documented (Ref. 14). It may occur as an impurity in any of the ingredients used in cosmetic lip products and externally applied cosmetics due to its background presence in the environment. Cosmetics manufacturers are responsible for avoiding potentially harmful levels of lead in their finished products. Our data show that over 99% of the cosmetic lip products and externally applied cosmetics on the U.S. market contain lead at levels below our recommended maximum level. Therefore, we encourage firms to continue the manufacturing practices that achieve these lower levels of lead in their finished products.

C. Enforcement Policy for Lead in Cosmetic Lip Products and Externally Applied Cosmetics

FDA is prepared to take enforcement action against any cosmetic lip product or externally applied cosmetic containing lead at levels that may harm consumers. FDA intends to consider several factors in bringing enforcement actions regarding lead in cosmetic lip products and externally applied cosmetics, including the level of lead present, the particular product, and the conditions of use for the product.

IV. References

We have placed the following references on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You may see them at that location between 9 a.m. and 4 p.m., Monday through Friday. As of December 20, 2016, FDA had verified the Web site address for the references it makes available as hyperlinks from the Internet copy of this guidance, but FDA is not responsible for any subsequent changes to Non-FDA Web site references after December 20, 2016.

1. International Cooperation on Cosmetics Regulation, "Considerations on Acceptable Lead Levels in Cosmetic Products," December 2013, available at http://iccrnet.org/topics/.

2. Health Canada, "Guidance on Heavy Metal Impurities in Cosmetics," July 20, 2012, available at http://www.hc-sc.gc.ca/cps-spc/pubs/indust/heavy_metals-metaux_lourds/index-eng.php.

3. Hepp, N. M., Mindak, W. R., and Cheng, J., "Determination of total lead in lipstick: Development and validation of a microwave-assisted digestion, inductively coupled plasma-mass

spectrometric method," Journal of Cosmetic Science, vol. 60, pp. 405-414, 2009.

4. Hepp, N. M., "Determination of total lead in 400 lipsticks on the U.S. market using a validated microwave-assisted digestion, inductively coupled plasma-mass spectrometric method," Journal of Cosmetic Science, vol. 63, pp. 159-176, 2012.

5. U.S. Food and Drug Administration, "Limiting Lead in Lipstick and Other Cosmetics," December 2016, available at http://www.fda.gov/Cosmetics/ProductsIngredients/Products/ucm137224.htm.

6. Hepp, N. M., Mindak, W. R., Gasper, J. W., Thompson, C. B., and Barrows, J. N., "Survey of cosmetics for arsenic, cadmium, chromium, cobalt, lead, mercury, and nickel content," Journal of Cosmetic Science, vol. 65, pp. 125-145, 2014.

7. U.S. Food and Drug Administration, "FDA's Testing of Cosmetics for Arsenic, Cadmium, Chromium, Cobalt, Lead, Mercury, and Nickel Content," December 2016, available at http://www.fda.gov/Cosmetics/ProductsIngredients/PotentialContaminants/ucm452836.htm.

8. Carrington, C. D., and Bolger, P. M., "An assessment of the hazards of lead in food," Regulatory Toxicology and Pharmacology, vol. 16, pp. 265-272, 1992.

9. Loretz, L. J., Api, A. M., Barraj, L. M., Burdick, J., Dressler, W. E., Gettings, S. D., Han Hsu, H., Pan, Y. H. L., Re, T. A., Renskers, K. J., Rothenstein, A.,, Scrafford, C. G., and Sewall, C., "Exposure data for cosmetic products: lipstick, body lotion, and face cream," Food and Chemical Toxicology, vol. 43, pp. 279-291, 2005.

10. Centers for Disease Control and Prevention, "National Health and Nutrition Examination Survey," available at http://www.cdc.gov/nchs/nhanes.htm.

11. Bress, W. C., and Bidanset, J. H., "Percutaneous in vivo and in vitro absorption of lead," Veterinary and Human Toxicology, vol. 33, pp. 212-214, 1991.

12. Loretz, L. J., Api, A. M. Api, Babcock, L., Barraj, L. M., Burdick, J., Cater, K. C., Jarrett, G., Mann, S., Pan, Y. H. L., Re, T. A., Renskers, K. J., and Scrafford, C. G., "Exposure data for cosmetic products: Facial cleanser, hair conditioner, and eye shadow," Food and Chemical Toxicology, vol. 46, pp. 1516–1524, 2008.

13. El Edelbi, R., Lindemalm, S., and Eksborg, S., "Estimation of body surface area in various childhood ages – validation of the Mosteller formula," Acta Pædiatrica, vol. 101, pp. 540-544, 2012.

14. Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry, "Toxicological Profile for Lead," available at http://www.atsdr.cdc.gov/ToxProfiles/tp13.pdf.

Guidance for Industry

Part 11, Electronic Records; Electronic Signatures — Scope and Application

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)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Applied Nutrition (CFSAN)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

August 2003
Pharmaceutical CGMPs

Guidance for Industry

Part 11, Electronic Records; Electronic Signatures — Scope and Application

Division of Drug Information, HFD-240
Center for Drug Evaluation and Research (CDER)
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
or
Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research (CBER)
http://www.fda.gov/cber/guidelines.htm
Phone: the Voice Information System at 800-835-4709 or 301-827-1800
or
Communications Staff (HFV-12),
Center for Veterinary Medicine (CVM)
(Tel) 301-594-1755
http://www.fda.gov/cvm/guidance/guidance.html
or
Division of Small Manufacturers Assistance (HFZ-220)
http://www.fda.gov/cdrh/ggpmain.html
Manufacturers Assistance Phone Number: 800.638.2041 or 301.443.6597
Internt'l Staff Phone: 301.827.3993
or
Center for Food Safety and Applied Nutrition (CFSAN)
http://www.cfsan.fda.gov/~dms/guidance.html.

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)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Applied Nutrition (CFSAN)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

August 2003
Pharmaceutical CGMPs

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for Industry[1]
Part 11, Electronic Records; Electronic Signatures — Scope and Application

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to describe the Food and Drug Administration's (FDA's) current thinking regarding the scope and application of part 11 of Title 21 of the Code of Federal Regulations; Electronic Records; Electronic Signatures (21 CFR Part 11).[2]

This document provides guidance to persons who, in fulfillment of a requirement in a statute or another part of FDA's regulations to maintain records or submit information to FDA,[3] have chosen to maintain the records or submit designated information electronically and, as a result, have become subject to part 11. Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations. Part 11 also applies to electronic records submitted to the Agency under the Federal Food, Drug, and Cosmetic Act (the Act) and the Public Health Service Act (the PHS Act), even if such records are not specifically identified in Agency regulations (§ 11.1). The underlying requirements set forth in the Act, PHS Act, and FDA regulations (other than part 11) are referred to in this guidance document as *predicate rules.*

[1] This guidance has been prepared by the Office of Compliance in the Center for Drug Evaluation and Research (CDER) in consultation with the other Agency centers and the Office of Regulatory Affairs at the Food and Drug Administration.

[2] 62 FR 13430

[3] These requirements include, for example, certain provisions of the Current Good Manufacturing Practice regulations (21 CFR Part 211), the Quality System regulation (21 CFR Part 820), and the Good Laboratory Practice for Nonclinical Laboratory Studies regulations (21 CFR Part 58).

As an outgrowth of its current good manufacturing practice (CGMP) initiative for human and animal drugs and biologics,[4] FDA is re-examining part 11 as it applies to all FDA regulated products. We anticipate initiating rulemaking to change part 11 as a result of that re-examination. This guidance explains that we will narrowly interpret the scope of part 11. While the re-examination of part 11 is under way, we intend to exercise enforcement discretion with respect to certain part 11 requirements. That is, we do not intend to take enforcement action to enforce compliance with the validation, audit trail, record retention, and record copying requirements of part 11 as explained in this guidance. However, records must still be maintained or submitted in accordance with the underlying predicate rules, and the Agency can take regulatory action for noncompliance with such predicate rules.

In addition, we intend to exercise enforcement discretion and do not intend to take (or recommend) action to enforce any part 11 requirements with regard to systems that were operational before August 20, 1997, the effective date of part 11 (commonly known as legacy systems) under the circumstances described in section III.C.3 of this guidance.

Note that part 11 remains in effect and that this exercise of enforcement discretion applies only as identified in this guidance.

FDA's guidance documents, including this guidance, 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. BACKGROUND

In March of 1997, FDA issued final part 11 regulations that provide criteria for acceptance by FDA, under certain circumstances, of electronic records, electronic signatures, and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper. These regulations, which apply to all FDA program areas, were intended to permit the widest possible use of electronic technology, compatible with FDA's responsibility to protect the public health.

After part 11 became effective in August 1997, significant discussions ensued among industry, contractors, and the Agency concerning the interpretation and implementation of the regulations. FDA has (1) spoken about part 11 at many conferences and met numerous times with an industry coalition and other interested parties in an effort to hear more about potential part 11 issues; (2) published a compliance policy guide, CPG 7153.17: Enforcement Policy: 21 CFR Part 11; Electronic Records; Electronic Signatures; and (3) published numerous draft guidance documents including the following:

[4] See *Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach* at www.fda.gov/oc/guidance/gmp.html.

- *21 CFR Part 11; Electronic Records; Electronic Signatures, Validation*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Glossary of Terms*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Time Stamps*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Maintenance of Electronic Records*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records*

Throughout all of these communications, concerns have been raised that some interpretations of the part 11 requirements would (1) unnecessarily restrict the use of electronic technology in a manner that is inconsistent with FDA's stated intent in issuing the rule, (2) significantly increase the costs of compliance to an extent that was not contemplated at the time the rule was drafted, and (3) discourage innovation and technological advances without providing a significant public health benefit. These concerns have been raised particularly in the areas of part 11 requirements for validation, audit trails, record retention, record copying, and legacy systems.

As a result of these concerns, we decided to review the part 11 documents and related issues, particularly in light of the Agency's CGMP initiative. In the *Federal Register* of February 4, 2003 (68 FR 5645), we announced the withdrawal of the draft guidance for industry, *21 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records*. We had decided we wanted to minimize industry time spent reviewing and commenting on the draft guidance when that draft guidance may no longer represent our approach under the CGMP initiative. Then, in the *Federal Register* of February 25, 2003 (68 FR 8775), we announced the withdrawal of the part 11 draft guidance documents on validation, glossary of terms, time stamps,[5] maintenance of electronic records, and CPG 7153.17. We received valuable public comments on these draft guidances, and we plan to use that information to help with future decision-making with respect to part 11. We do not intend to re-issue these draft guidance documents or the CPG.

We are now re-examining part 11, and we anticipate initiating rulemaking to revise provisions of that regulation. To avoid unnecessary resource expenditures to comply with part 11 requirements, we are issuing this guidance to describe how we intend to exercise enforcement discretion with regard to certain part 11 requirements during the re-examination of part 11. As mentioned previously, part 11 remains in effect during this re-examination period.

III. DISCUSSION

A. Overall Approach to Part 11 Requirements

[5] Although we withdrew the draft guidance on time stamps, our current thinking has not changed in that when using time stamps for systems that span different time zones, we do not expect you to record the signer's local time. When using time stamps, they should be implemented with a clear understanding of the time zone reference used. In such instances, system documentation should explain time zone references as well as zone acronyms or other naming conventions.

As described in more detail below, the approach outlined in this guidance is based on three main elements:

- Part 11 will be interpreted narrowly; we are now clarifying that fewer records will be considered subject to part 11.
- For those records that remain subject to part 11, we intend to exercise enforcement discretion with regard to part 11 requirements for validation, audit trails, record retention, and record copying in the manner described in this guidance and with regard to all part 11 requirements for systems that were operational before the effective date of part 11 (also known as legacy systems).
- We will enforce all predicate rule requirements, including predicate rule record and recordkeeping requirements.

It is important to note that FDA's exercise of enforcement discretion as described in this guidance is limited to specified part 11 requirements (setting aside legacy systems, as to which the extent of enforcement discretion, under certain circumstances, will be more broad). We intend to enforce all other provisions of part 11 including, but not limited to, certain controls for closed systems in § 11.10. For example, we intend to enforce provisions related to the following controls and requirements:

- limiting system access to authorized individuals
- use of operational system checks
- use of authority checks
- use of device checks
- determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
- establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
- appropriate controls over systems documentation
- controls for open systems corresponding to controls for closed systems bulleted above (§ 11.30)
- requirements related to electronic signatures (e.g., §§ 11.50, 11.70, 11.100, 11.200, and 11.300)

We expect continued compliance with these provisions, and we will continue to enforce them. Furthermore, persons must comply with applicable predicate rules, and records that are required to be maintained or submitted must remain secure and reliable in accordance with the predicate rules.

B. Details of Approach – Scope of Part 11

1. Narrow Interpretation of Scope

We understand that there is some confusion about the scope of part 11. Some have understood the scope of part 11 to be very broad. We believe that some of those broad interpretations could

lead to unnecessary controls and costs and could discourage innovation and technological advances without providing added benefit to the public health. As a result, we want to clarify that the Agency intends to interpret the scope of part 11 narrowly.

Under the narrow interpretation of the scope of part 11, with respect to records required to be maintained under predicate rules or submitted to FDA, when persons choose to use records in electronic format in place of paper format, part 11 would apply. On the other hand, when persons use computers to generate paper printouts of electronic records, and those paper records meet all the requirements of the applicable predicate rules and persons rely on the paper records to perform their regulated activities, FDA would generally not consider persons to be "using electronic records in lieu of paper records" under §§ 11.2(a) and 11.2(b). In these instances, the use of computer systems in the generation of paper records would not trigger part 11.

2. Definition of Part 11 Records

Under this narrow interpretation, FDA considers part 11 to be applicable to the following records or signatures in electronic format (part 11 records or signatures):

- Records that are required to be maintained under predicate rule requirements and that are maintained in electronic format *in place of paper format*. On the other hand, records (and any associated signatures) that are not required to be retained under predicate rules, but that are nonetheless maintained in electronic format, are not part 11 records.

  We recommend that you determine, based on the predicate rules, whether specific records are part 11 records. We recommend that you document such decisions.

- Records that are required to be maintained under predicate rules, that are maintained in electronic format *in addition to paper format,* and that *are relied on to perform regulated activities*.

  In some cases, actual business practices may dictate whether you are *using* electronic records instead of paper records under § 11.2(a). For example, if a record is required to be maintained under a predicate rule and you use a computer to generate a paper printout of the electronic records, but you nonetheless rely on the electronic record to perform regulated activities, the Agency may consider you to be *using* the electronic record instead of the paper record. That is, the Agency may take your business practices into account in determining whether part 11 applies.

  Accordingly, we recommend that, for each record required to be maintained under predicate rules, you determine in advance whether you plan to rely on the electronic record or paper record to perform regulated activities. We recommend that you document this decision (e.g., in a Standard Operating Procedure (SOP), or specification document).

- Records submitted to FDA, under predicate rules (even if such records are not specifically identified in Agency regulations) in electronic format (assuming the records have been identified in docket number 92S-0251 as the types of submissions the Agency accepts in electronic format). However, a record that is not itself submitted, but is used

in generating a submission, is not a part 11 record unless it is otherwise required to be maintained under a predicate rule and it is maintained in electronic format.

- Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules. Part 11 signatures include electronic signatures that are used, for example, to document the fact that certain events or actions occurred in accordance with the predicate rule (e.g. *approved*, *reviewed*, and *verified*).

C. Approach to Specific Part 11 Requirements

1. Validation

The Agency intends to exercise enforcement discretion regarding specific part 11 requirements for validation of computerized systems (§ 11.10(a) and corresponding requirements in § 11.30). Although persons must still comply with all applicable predicate rule requirements for validation (e.g., 21 CFR 820.70(i)), this guidance should not be read to impose any additional requirements for validation.

We suggest that your decision to validate computerized systems, and the extent of the validation, take into account the impact the systems have on your ability to meet predicate rule requirements. You should also consider the impact those systems might have on the accuracy, reliability, integrity, availability, and authenticity of required records and signatures. Even if there is no predicate rule requirement to validate a system, in some instances it may still be important to validate the system.

We recommend that you base your approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity. For instance, validation would not be important for a word processor used only to generate SOPs.

For further guidance on validation of computerized systems, see FDA's guidance for industry and FDA staff *General Principles of Software Validation* and also industry guidance such as the *GAMP 4 Guide* (See References).

2. Audit Trail

The Agency intends to exercise enforcement discretion regarding specific part 11 requirements related to computer-generated, time-stamped audit trails (§ 11.10 (e), (k)(2) and any corresponding requirement in §11.30). Persons must still comply with all applicable predicate rule requirements related to documentation of, for example, date (e.g., § 58.130(e)), time, or sequencing of events, as well as any requirements for ensuring that changes to records do not obscure previous entries.

Even if there are no predicate rule requirements to document, for example, date, time, or sequence of events in a particular instance, it may nonetheless be important to have audit trails or other physical, logical, or procedural security measures in place to ensure the trustworthiness and

reliability of the records.[6] We recommend that you base your decision on whether to apply audit trails, or other appropriate measures, on the need to comply with predicate rule requirements, a justified and documented risk assessment, and a determination of the potential effect on product quality and safety and record integrity. We suggest that you apply appropriate controls based on such an assessment. Audit trails can be particularly appropriate when users are expected to create, modify, or delete regulated records during normal operation.

3. Legacy Systems[7]

The Agency intends to exercise enforcement discretion with respect to all part 11 requirements for systems that otherwise were operational prior to August 20, 1997, the effective date of part 11, under the circumstances specified below.

This means that the Agency does not intend to take enforcement action to enforce compliance with any part 11 requirements if all the following criteria are met for a specific system:

- The system was operational before the effective date.
- The system met all applicable predicate rule requirements before the effective date.
- The system currently meets all applicable predicate rule requirements.
- You have documented evidence and justification that the system is fit for its intended use (including having an acceptable level of record security and integrity, if applicable).

If a system has been changed since August 20, 1997, and if the changes would prevent the system from meeting predicate rule requirements, Part 11 controls should be applied to Part 11 records and signatures pursuant to the enforcement policy expressed in this guidance.

4. Copies of Records

The Agency intends to exercise enforcement discretion with regard to specific part 11 requirements for generating copies of records (§ 11.10 (b) and any corresponding requirement in §11.30). You should provide an investigator with reasonable and useful access to records during an inspection. All records held by you are subject to inspection in accordance with predicate rules (e.g., §§ 211.180(c), (d), and 108.35(c)(3)(ii)).

We recommend that you supply copies of electronic records by:

- Producing copies of records held in common portable formats when records are maintained in these formats
- Using established automated conversion or export methods, where available, to make copies in a more common format (examples of such formats include, but are not limited to, PDF, XML, or SGML)

[6] Various guidance documents on information security are available (see References).

[7] In this guidance document, we use the term *legacy system* to describe systems already in operation before the effective date of part 11.

In each case, we recommend that the copying process used produces copies that preserve the content and meaning of the record. If you have the ability to search, sort, or trend part 11 records, copies given to the Agency should provide the same capability if it is reasonable and technically feasible. You should allow inspection, review, and copying of records in a human readable form at your site using your hardware and following your established procedures and techniques for accessing records.

5. Record Retention

The Agency intends to exercise enforcement discretion with regard to the part 11 requirements for the protection of records to enable their accurate and ready retrieval throughout the records retention period (§ 11.10 (c) and any corresponding requirement in §11.30). Persons must still comply with all applicable predicate rule requirements for record retention and availability (e.g., §§ 211.180(c),(d), 108.25(g), and 108.35(h)).

We suggest that your decision on how to maintain records be based on predicate rule requirements and that you base your decision on a justified and documented risk assessment and a determination of the value of the records over time.

FDA does not intend to object if you decide to archive required records in electronic format to nonelectronic media such as microfilm, microfiche, and paper, or to a standard electronic file format (examples of such formats include, but are not limited to, PDF, XML, or SGML). Persons must still comply with all predicate rule requirements, and the records themselves and any copies of the required records should preserve their content and meaning. As long as predicate rule requirements are fully satisfied and the content and meaning of the records are preserved and archived, you can delete the electronic version of the records. In addition, paper and electronic record and signature components can co-exist (i.e., a hybrid[8] situation) as long as predicate rule requirements are met and the content and meaning of those records are preserved.

[8] Examples of hybrid situations include combinations of paper records (or other nonelectronic media) and electronic records, paper records and electronic signatures, or handwritten signatures executed to electronic records.

IV. REFERENCES

Food and Drug Administration References

1. *Glossary of Computerized System and Software Development Terminolo*gy (Division of Field Investigations, Office of Regional Operations, Office of Regulatory Affairs, FDA 1995) (http://www. fda.gov/ora/inspect_ref/igs/gloss.html)

2. *General Principles of Software Validation; Final Guidance for Industry and FDA Staff* (FDA, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research, 2002) (http://www.fda.gov/cdrh/comp/guidance/938.html)

3. *Guidance for Industry, FDA Reviewers, and Compliance on Off-The-Shelf Software Use in Medical Devices* (FDA, Center for Devices and Radiological Health, 1999) (http://www.fda.gov/cdrh/ode/guidance/585.html)

4. *Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach* (FDA 2002) (http://www.fda.gov/oc/guidance/gmp.html)

Industry References

1. *The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems, GAMP 4* (ISPE/GAMP Forum, 2001) (http://www.ispe.org/gamp/)

2. ISO/IEC 17799:2000 (BS 7799:2000) Information technology – Code of practice for information security management (ISO/IEC, 2000)

3. ISO 14971:2002 Medical Devices- Application of risk management to medical devices (ISO, 2001)

Contains Nonbinding Recommendations

Guidance for Industry
Safety of Nanomaterials in Cosmetic Products

You may submit either electronic or written comments regarding this guidance at any time. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact the Center for Food Safety and Applied Nutrition (CFSAN) at 240-402-1130.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition

June 2014

Contains Nonbinding Recommendations

Table of Contents

Contains Nonbinding Recommendations

Guidance for Industry[1]

Safety of Nanomaterials in Cosmetic Products

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

I. Introduction

This document provides guidance to industry and other stakeholders (e.g., academia, other regulatory groups) on FDA's current thinking on the safety assessment of nanomaterials in cosmetic products. The guidance document is intended to assist industry and other stakeholders in identifying the potential safety issues of nanomaterials in cosmetic products and developing a framework for evaluating them. This guidance also provides contact information for manufacturers and sponsors who wish to discuss safety considerations regarding the use of specific nanomaterials in cosmetic products with FDA. This guidance is not applicable to other products regulated by FDA, including over-the-counter and prescription drugs and medical devices.

FDA's guidance documents, including this guidance, 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 our guidances means that something is suggested or recommended, but not required.

II. Background

Nanomaterials are used in a variety of FDA-regulated products because of their unique properties, imparting potential advantages to products considered for development. Such materials, due to their nanoscale size, can have chemical, physical, and biological properties that differ from those of their larger counterparts. Such differences may include altered magnetic properties, altered electrical or optical activity, increased structural integrity, or altered chemical or biological activity (Ref. 1). These new or altered properties may affect the performance, quality, safety, and/or effectiveness, if applicable, of a product that incorporates that nanomaterial.

[1] This guidance has been prepared by the Office of Cosmetics and Colors in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

In July of 2007, FDA issued a report prepared by its Nanotechnology Task Force ("Task Force"). The Task Force report presented an assessment of scientific and regulatory considerations relating to the safety and effectiveness of FDA-regulated products containing nanomaterials and made recommendations in light of these considerations (Ref. 2). Specifically, with respect to cosmetic products, the Task Force recommended that we issue guidance describing safety issues that manufacturers should consider to ensure that cosmetic products made with nanomaterials are safe and not adulterated. We are issuing this guidance as part of our ongoing efforts to implement the Task Force recommendations (Ref. 2).

The Task Force also recommended that FDA request submission of data and other information addressing the effects of nanomaterials in those products that are not subject to premarket authorization, such as cosmetic products. On September 8, 2008, FDA held a public meeting to discuss such data and information, along with related scientific and regulatory issues concerning nanotechnology. FDA considered the information obtained at, and subsequent to, the public meeting in developing this guidance. We also considered information provided by the cosmetic industry to the International Cooperation on Cosmetics Regulations (ICCR), publications and information regarding recent advances in nanotechnology, and other authoritative guidance/ reports regarding the safety of nanomaterials (Refs. 3, 4, 5, 6). This guidance also refers to other relevant reports, such as the Organization for Economic Co-operation and Development (OECD) Working Party on Manufactured Nanomaterials "Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials" (Ref. 7), the Scientific Committee on Consumer Safety (SCCS) "Guidance on the Safety Assessment of Nanomaterials in Cosmetics" (Ref. 8), and relevant ICCR reports, such as on the "Currently Available Methods for Characterization of Nanomaterials," and "Principles of Cosmetic Product Safety Assessment." (Refs. 9, 10).

FDA has not established regulatory definitions of "nanotechnology," "nanomaterial," "nanoscale," or other related terms. In June 2014, FDA issued a guidance for industry titled "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology" (Ref. 1). As described in that guidance, 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); and (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 cosmetic products.

The application of nanotechnology may result in product attributes that differ from those of conventionally-manufactured products, and thus may merit particular examination. However, we do not categorically judge all products containing nanomaterials or otherwise involving application of nanotechnology as intrinsically benign or harmful. Rather, for

nanotechnology-derived and conventionally-manufactured cosmetic products alike, we consider the characteristics of the finished product and the safety for its intended use. Our consideration of nanotechnology applications in cosmetic products in this document is consistent with the agency guidance (Ref. 1) and with the broader federal guidance on regulatory oversight of emerging technologies (Ref. 11) and nanotechnology (Ref. 12).

III. Discussion

A. General Framework for Assessing the Safety of Nanomaterials in Cosmetic Products

Section 301(a) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 331(a)) prohibits the marketing of adulterated or misbranded cosmetics[2] in interstate commerce. The FD&C Act does not subject cosmetics or cosmetic ingredients (with the exception of color additives) to FDA premarket approval in order to be marketed legally in the United States. Except for color additives and those ingredients that are prohibited or restricted from use in cosmetics by regulation, a manufacturer may use any ingredient in the formulation of a cosmetic provided that the use of the ingredient does not otherwise cause the cosmetic to be adulterated (section 601 of the FD&C Act (21 U.S.C. 361)) or misbranded (section 602 of the FD&C Act (21 U.S.C. 362)).[3]

Cosmetic product manufacturers must ensure that the product is not misbranded or adulterated. The FD&C Act does not give us the authority to require that safety data be submitted to us or to approve a cosmetic product before it is marketed. Nevertheless, manufacturers or distributors are responsible for obtaining all data and information needed to substantiate the safety of their products before introducing them into the marketplace.

In the Federal Register of March 3, 1975 (40 FR 8912 at 8916), we advised that "the safety of a product can be adequately substantiated through (a) reliance on already available toxicological test data on individual ingredients and on product formulations that are similar in composition to the particular cosmetic, and (b) performance of any additional toxicological and other tests that are appropriate in light of such existing data and information. Although satisfactory toxicological data may exist for each ingredient of a cosmetic product, it will still be necessary to conduct some toxicological testing with the complete formulation to assure adequately the safety of the finished cosmetic."

We believe that these general principles are applicable to the safety substantiation of cosmetic products whether they contain nanomaterials or conventionally manufactured

[2] The FD&C Act defines cosmetics by their intended use as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness or altering the appearance, and articles intended for use as a component of any such articles; except that such term shall not include soap" (section 201(i) of the FD&C Act).

[3] The name of each ingredient must be declared on the label of the cosmetic product, as required by 21 CFR 701.3.

ingredients. In applying these principles, however, it may be important to give particular consideration to the fact that a material at nanoscale may show changes in, or have novel, physicochemical properties, behaviors, and/or effects that could be different from a larger scale material with the same chemical composition (Refs. 2, 8).

For example, the small particle size of a nanomaterial has the potential to alter the distribution and bioavailability of that material compared to a larger scale material with the same chemical composition. The small size leads to increased surface area relative to the mass of the particle, which could result in increased biological interactions. In addition, the uptake, absorption, and biodistribution of the material may be altered, leading to potential systemic exposure (Refs. 5, 8).

In some cases, the traditional testing methods that have been used to determine the safety of cosmetic ingredients and finished products may not be fully applicable due to a nanomaterial's distinctive properties and behavior. Such distinctive physicochemical characteristics or biological interactions may affect the results or interpretation of results obtained from traditional toxicology testing, which form an integral part of safety substantiation. In Section III.B of this document, we highlight key scientific considerations relevant to the assessment of the safety of nanomaterials used in cosmetic products.

If you wish to use a nanomaterial in a cosmetic product, either a new material or an altered version of an already marketed ingredient, we encourage you to meet with us to discuss the test methods and data that might help substantiate the product's safety, including short-term toxicity and long-term toxicity data, as appropriate. We encourage you to contact us to discuss any aspect of the safety assessment of cosmetic ingredients or finished products.

B. Points to Consider in Assessing the Safety of Nanomaterials in Cosmetic Products

We consider the current framework for safety assessment sufficiently robust and flexible to be appropriate for a variety of materials, including products containing nanomaterials. Just as the traditional safety assessment includes material characterization and toxicology considerations, safety evaluations of cosmetic products containing nanomaterials should also take these considerations into account. As noted in section III.A, nanomaterials may exhibit new or altered physicochemical properties that may affect biological interactions, which may raise questions about the safety of the product containing nanomaterials. Any such unique properties or biological effects of nanomaterials should be identified and appropriately addressed during safety evaluations.

With respect to nanomaterial characterization, safety should be assessed through fully describing the nanomaterial and evaluating a wide range of physical and chemical properties, as well as through the assessment of impurities, if present. The toxicology and absorption, distribution, metabolism, and excretion considerations for nanomaterials in cosmetic products can be informed by addressing the routes of exposure, the uptake and

absorption, and toxicity testing. In addition, any distinctive properties and biological behavior of nanomaterials should be considered in determining the suitability of traditional testing methods for toxicity testing of cosmetic products containing nanomaterials. As needed, traditional toxicity testing methods should be modified or new methods developed to address: (1) the key chemical and physical properties that may affect the toxicity profile of nanomaterials and (2) the effects of those properties on the function of the cosmetic formulation. The toxicological testing should include consideration of toxicity of both the ingredients and impurities; dosimetry for *in vitro* and *in vivo* toxicology studies, if needed; clinical testing, if warranted; and toxicokinetics and toxicodynamics. The overall package of data and information should substantiate the safety of the product under the intended conditions of use. These considerations are discussed in greater detail in sections III.B.1 and III.B.2 below.

1. Nanomaterial Characterization

Nanomaterials vary widely in composition, morphology, and other characteristics and cannot be considered a uniform group of substances. These substances may have physical, chemical, or biological properties that are different from those of larger scale material with the same chemical composition. As stated earlier, such differences may include altered magnetic properties, altered electrical or optical activity, increased structural integrity, or altered chemical or biological activity (Ref. 6).

As discussed in the FDA Task Force report, studies indicate that various attributes of a particular nanoscale material, including increased surface-area-to-volume ratio, morphology, surface features, and charge, can affect the distribution of that material in the body and that material's interaction with biological systems (Ref. 2, 8). Therefore, thorough characterization of nanomaterials can form an integral part of the safety assessment. This would include proper identification of the chemical composition as well as impurities, structure, and configuration of the nanomaterial(s) used in the cosmetic product. In addition, characterization of the nanomaterial(s) as present in the raw material, formulation, test media, and in the relevant biological environment for toxicological testing should be considered to help determine potential biological interactions and effects (Ref. 8). In addition, stability of the nanomaterial under testing conditions and in a formulation under intended conditions of use should be determined.

a. Physicochemical Properties

As with any cosmetic ingredient, the nanomaterial should be fully described, including:

- the nanomaterial name,
- the Chemical Abstracts Service (CAS) number,
- the structural formula,
- the elemental and molecular composition including:

- the degree of purity, and
- any known impurities or additives.

A thorough understanding of the details of the manufacturing process will help identify residual additives and impurities, as well as certain other physical and chemical properties. A wide range of physical and chemical properties should be evaluated to help determine if a substance produced with nanotechnology is safe for the proposed use (Refs. 7, 13, 14, 15). Proper characterization should include, as appropriate:

- measurement of particle size and distribution,
- aggregation and agglomeration characteristics,
- surface chemistry, including:
  - zeta potential/surface charge,
  - surface coating,
  - functionalization, and
  - catalytic activity
- morphology including:
  - shape,
  - surface area,
  - surface topology, and
  - crystallinity
- solubility,
- density,
- stability, and
- porosity.

Although a wide range of analytical techniques are available for measurement of physicochemical properties of materials (Refs. 8, 9, 16), many of these methods have not been validated for the evaluation of nanomaterials in cosmetic products. Therefore, appropriate analytical methods suitable for the specific nanomaterial and the cosmetic product formulation should be chosen, and results obtained from such tests appropriately interpreted and reported for adequate characterization of the material.

b. Impurities

As with any cosmetic ingredient, a change in the starting material used to prepare a formulation will likely result in altered composition of the final product, which may result in different impurities. Variables such as altered purity or changes in the starting material should be considered. A manufacturer should assess the identity and quantity of impurities and how they may affect the overall safety of the end product.

It is also important to understand how the nanomaterial is manufactured. Nanoscale impurities may arise from the manufacturing process. Changes in the manufacturing

process, including use of different solvents, time/temperature conditions and changes to the starting chemicals (*e.g.,* alternative starting materials, different purity levels or different concentrations of the chemicals used in the process) may change the types and/or quantities of impurities in the final product. Additional agents, such as dispersing agents and surface modifiers, are often used in the manufacture of nanomaterials. These additional agents and impurities should be considered in the safety substantiation for nanomaterials in cosmetic products.

2. Toxicology Considerations

The appropriateness of toxicological testing depends on the intended use, exposure levels, and degree of concern for potential toxicity of an ingredient or formulation. In determining what toxicological testing may be appropriate, manufacturers should consider each ingredient's chemical structure and composition, and physicochemical properties, purity/impurities, agglomeration and size distribution, stability, conditions of exposure, uptake and absorption, bioavailability, toxicity, and any other qualities that may affect the safety of the product for its intended use. Manufacturers should address both short-term and long-term toxicity of nanomaterials (Ref. 8), and consider the need to evaluate the possibility of ingredient-ingredient interactions or ingredient-packaging interactions.

Where traditional toxicity test methods are used, manufacturers should consider the applicability of the test methods and, as needed, modify them with respect to such factors as appropriate solvents and dosing formulations, solubility, agglomeration and aggregation of particles, and stability conditions associated with the cosmetic product containing nanomaterials (Refs. 2, 17, 18). For example, whether a nanomaterial is soluble, insoluble, or partially-soluble may affect the suitability of a traditional toxicity test method. Some traditional *in vivo* test methods may be suitable for only soluble nanomaterials (Ref. 17). Some traditional *in vitro* and *in vivo* test methods may need to be adjusted for testing insoluble or partially-soluble nanomaterials (Refs. 7, 18). These considerations are important because nanoparticles tend to stick to each other to form larger agglomerates/aggregates that may be insoluble. Therefore, in a dosing or test medium, nanomaterials may be present as a nano-dispersion rather than in solution (Refs. 7, 18). Agglomeration and aggregation of particles is another factor that may affect the suitability of traditional toxicity testing methods, and manufacturers should ensure that testing appropriately reflects the range of free particles and any aggregates or aggolomerates found in the cosmetic product formulation. Toxicological testing may need to be conducted separately on the free nanoparticles and the agglomerated/aggregated nanoparticles because they will likely have different chemical and biological properties. Due to their high surface energy, nanomaterials may also interact with the testing medium or bind to different substances, including proteins, in the test medium, resulting in an altered biological activity (Refs. 8, 19, 20, 21). Thus, manufacturers should consider and make necessary adjustments to traditional toxicity testing methods, taking into account the specific characteristics of the nanomaterial as it is intended to be used in the cosmetic product. In instances where traditional toxicity testing methods cannot be satisfactorily modified, FDA recommends developing new methods to adequately assess the toxicity of the nanomaterial in the cosmetic product and ensure the product is safe.

It is also important to mention that the dose metrics currently used for toxicological testing of conventionally manufactured chemicals (measured and expressed in mass, volume or number of particles such as mg/kg, or mg/L) may not be appropriate for nanomaterials because of their large surface area per particle mass or volume (Refs. 5, 8). In addition to weight/volume metrics, evaluations of the safety of nanomaterials should also consider alternative metrics, such as weight/volume concentration, particle number concentration and surface area, until suitable parameters for dose metrics become available.

a. Routes of Exposure

The safety of an ingredient is based in part on the potential for exposure and the relevant routes of exposure that are determined by its intended use and its application. Although most cosmetic products are applied directly to the skin, some products may be applied by spray presenting the possibility of inhalation exposure. Additionally, some cosmetic products are applied in an area where there is the possibility of oral exposure. Additionally, systemic absorption can result from dermal, inhalation, ocular and oral exposures (Refs. 22, 23). Therefore, for nanomaterials, the dose to the primary exposure organs as well as the dose to any secondary target organs should be considered in developing or modifying toxicological testing methods and for evaluating the test data (Ref. 5).

b. Uptake and Absorption

As stated above, some nanomaterials have unique physicochemical properties that may alter the potential toxicity of a compound (e.g. reduction in particle size could increase the ability for the compound to be absorbed). Therefore, the safety assessment should address whether there will be an increase in uptake, absorption, transport into cells, and transport across barriers (e.g. blood-brain barrier) or altered bioavailability or biological half-life. For example, there may be an increase in the dose delivered to sensitive tissues due to the increased ability of the nanomaterial to pass through the blood-brain barrier (Ref. 24).

Nanomaterials used in cosmetic products can be divided into two groups: (1) soluble and/or biodegradable nanoparticles, which disintegrate into their molecular components (e.g. some liposomes and nanoemulsions) upon application to skin and thus may not raise safety questions, and (2) insoluble, sufficiently stable and/or biopersistent nanoparticles (e.g. titanium dioxide (TiO_2), fullerenes, and quantum dots). Some insoluble, partially-soluble or sufficiently stable nanomaterials, particularly those in the lower nanoscale range and with certain surface characteristics, may be able to cross biological membrane barriers (Ref. 25) and may have harmful effects due to the potential interaction with organs and cellular compartments. Thus, when there is evidence of systemic exposure to nanomaterials, manufacturers should consider including absorption, distribution, metabolism, and excretion (ADME) parameters in safety assessments of the nanomaterial in the cosmetic product (Ref. 8).

For exposure via dermal absorption, studies should be conducted with both intact skin and impaired skin (e.g. sunburned, atopic, eczematous, psoriatic, or systematically damaged skin)

to address the possibility of an increased rate of penetration and ability of the ingredient to become systemically absorbed. The passive transport of many nanomaterials may not occur through intact skin, but there is an increased probability for entry of nanomaterials through skin with an impaired barrier layer (Refs. 26, 27). A variety of techniques used to study and quantify skin penetration of chemicals are discussed in the literature (Refs. 28, 29). We recognize that there are limitations to using impaired skin models for conducting dermal absorption studies as there is currently no standard or established method(s). We encourage manufacturers to develop appropriate impaired skin models for dermal absorption studies.

The use of aerosolized cosmetic products can also result in exposure to nanomaterials via the respiratory tract. The deposition of nanomaterials in the respiratory system depends on their aerosol properties and interactions with respiratory epithelium. The soluble nanoparticles may be dissolved, metabolized and transported to other organs and blood whereas the insoluble nanoparticles may be either retained in the airways and result in pulmonary effects or swallowed by coughing and cleared. As discussed earlier, the physical characteristics, including surface properties of nanomaterials, are important factors that warrant careful attention, particularly for inhaled nanoscale particles. Studies have indicated that decreasing the size of particles and increasing the surface area can result in potential adverse effects not only in the respiratory system, but also in the heart and blood vessels, the central nervous system, and the immune system (Ref. 30).

Exposure via the oral route is generally limited to those products that are introduced into or applied near the mouth (e.g., mouthwash, lipsticks). Limited evidence suggests that the uptake of nanomaterials and systemic absorption depends on their size, surface charge, and surface ligand modification (Ref. 30). Additional studies have indicated that nanomaterials have limited uptake in the gastrointestinal tract, but the translocation to certain regions of the intestinal barrier can be substantially increased (Refs. 31, 32).

Therefore, we recommend that the safety assessment process for nanomaterials include the issues of toxicokinetics and toxicodynamics with reference to different exposure routes.

c. Toxicity Testing

The initial step in the evaluation of the safety assessment of cosmetic products is to conduct toxicity testing based on a toxicological profile of the ingredients and their routes of exposure. There are several guidelines (Refs. 4, 33, 34) for conducting toxicity testing (tiered testing strategy) of chemicals that can be used as a starting point in evaluating toxicity of nanomaterial ingredients. Consistent with the guidelines issued by the Cosmetic, Toiletry and Fragrance Association (CTFA) (Ref. 33) and the Organization for Economic Co-operation and Development (OECD) (Ref. 3), we recommend, at a minimum, testing for acute toxicity, skin irritation, ocular irritation, dermal photoirritation, skin sensitization, mutagenicity/ genotoxicity, repeated dose (21-28 days) toxicity, and subchronic (90 days) toxicity (Ref. 34). We also recommend phototoxicity testing (Ref. 35) for a cosmetic product that is intended to be used on sun-exposed skin. Results obtained from this basic test battery may indicate a need for additional testing. Where available, other relevant data, such as toxicological data on individual ingredients that are

similar in composition to the nanomaterial or data on a larger scale material with the same chemical composition as the nanomaterial, can also be considered.

As stated previously, in designing tests for use with nanomaterials in cosmetics products, manufacturers should consider modifying traditional toxicity testing with respect to such factors as appropriate solvents and dosing formulations, agglomeration of particles, purity and stability conditions, and other variables. New methods may also need to be developed if traditional tests cannot be modified satisfactorily. For example, the Ames test, recommended as part of a battery of genotoxicity testing for conventional chemicals, may not be suitable for insoluble or partially-soluble nanomaterials used in cosmetic products because the bacterial cell wall may create a possible barrier for many nanomaterials (Ref. 36).

Toxicity testing *in vivo* has long been considered indispensable for obtaining information on translocation, biodistribution, accumulation, and clearance (Ref. 37). As mentioned earlier, while conducting *in vivo* toxicity testing for nanomaterials, careful attention should be paid to the issue of dose metrics (mass, volume or number of particles). The manufacturer should consider the surface area and number of particles, as well as mass concentration in the study design of *in vivo* toxicity testing. For *in vivo* studies via the dermal route of administration, the test substance should be applied directly to the skin, and for the oral route of administration, the test substance should be given either by gavage or in the diet. Agglomeration or aggregation characteristics of nanomaterials in the topical vehicle, gavage or feed matrix are other important factors to assess prior to conducting these studies for safety assessment. Additionally, the potential for nanomaterials to penetrate through the skin or be absorbed through the gut and becoming available for biodistribution, should be addressed while estimating the risks associated with the exposure to nanomaterials.

There has been recent emphasis on the development of validated methods for *in vitro* testing of cosmetic products by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the European Center for the Validation of Alternative Methods (ECVAM). The seventh amendment to Directive 2003/15/EC of the European Parliament and of the Council (Ref. 38) instituted a ban on animal testing of cosmetic products in 2004 and a ban on certain animal tests with validated alternatives in March 2009. We recommend validation of *in vitro* methods for safety testing of cosmetic products and ingredients and optimizing these models for nanomaterials, with particular attention being paid to the issues of cytotoxicity and precipitation of insoluble ingredients. Nanomaterials can settle, diffuse, and aggregate differentially according to their size, density, and surface chemistry (Ref. 39). Thus, the assessment of the agglomeration or aggregation of nanomaterials in the media used in the *in vitro* system should be addressed.

Alternative testing methods currently under consideration that can be optimized for a specific nanomaterial and might be useful to help determine ingredient safety include:

1. Reconstructed human skin such as Episkin™ and Epiderm ™ for skin irritation and corrosion testing;

2. Phototoxicity testing via 3T3 NRPT (3T3 fibroblasts neutral red uptake phototoxicity testing) applicable to ultra violet (UV) absorbing substances;
3. Human/pig skin in a diffusion cell for dermal absorption;
4. Bovine Corneal Opacity and Permeability (BCOP) and the Isolated Chicken Eye (ICE) for ocular irritation; and
5. Genotoxicity testing using a battery of recommended tests covering the endpoints of gene mutation, and structural and numerical aberrations. While conducting genotoxicty tests, the nanomaterial's specific properties should be taken into account to understand the mechanism of nanomaterials' genotoxic effects (Ref. 36).

Finally, we note that *in vivo* studies may be more suitable for nanomaterials with limited solubility properties (Ref. 8).

C. Summary of Recommendations

In summary, nanomaterials can have chemical, physical, and biological properties that differ from those of larger scale particles with the same chemical composition, and the use of nanomaterials in cosmetic products may raise questions about the safety of the product for its intended use. As with any cosmetic product that has new or altered properties, data needs and testing methods should be evaluated to address any unique properties and function of the nanomaterials used in the cosmetic products as well as the questions that continue to remain about the applicability of traditional safety testing methods to products that involve nanotechnology. We recommend that the safety assessment for cosmetic products using nanomaterials should address several important factors, including:

- the physicochemical characteristics,
- agglomeration and size distribution of nanomaterials under the conditions of toxicity testing and as expected in the final product,
- impurities,
- potential routes of exposure to the nanomaterials,
- potential for aggregation and agglomeration of nanoparticles in the final product,
- dosimetry for *in vitro* and *in vivo* toxicology studies, and
- *in vitro* and *in vivo* toxicological data on nanomaterial ingredients and their impurities, dermal penetration, potential inhalation, irritation (skin and eye) and sensitization studies, mutagenicity/genotoxicity studies.

We expect that the science surrounding nanomaterials will continue to evolve and be used in the development of new testing methods.

The safety of a cosmetic product should be evaluated by analyzing the physicochemical properties and the relevant toxicological endpoints of each ingredient in relation to the expected exposure resulting from the intended use of the finished product. If you wish to use a nanomaterial in a cosmetic product, either a new material or an altered version of an

already marketed ingredient, we encourage you to meet with us to discuss the test methods and data needed to substantiate the product's safety, including short-term toxicity and other long-term toxicity data, as appropriate. We welcome your questions relating to the use of nanomaterials in cosmetic products.

IV. How to Contact FDA About this Guidance

Contact the Office of Cosmetics and Colors at 240-402-1130 if you have questions or would like to meet with us. You may also contact FDA by email at industry.cosmetics@fda.gov.

V. References

We have placed these references on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You may see them at that location between 9 a.m. and 4 p.m., Monday through Friday. As of June 3rd , 2014 FDA had verified the Web site addresses for the references it makes available as hyperlinks from the Internet copy of this guidance, but FDA is not responsible for any subsequent changes to Non- FDA Web site references after June 23rd , 2014.

1. FDA. 2013. Guidance for Industry. Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology, available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm.
2. FDA. 2007. A Report of the U.S. Food and Drug Administration Nanotechnology Task Force. As of the date of this guidance, this Web site is an active site that adds information over time to provide the most current information about this topic. Persons who access this Web site after June 23rd may find more information than the information we placed in the Division of Dockets Management.
3. Scientific Committee on Emerging and Newly-Identified Health Risks Opinion on the Appropriateness of the Risk Assessment Methodology in accordance with the Technical Guidance Documents for New and Existing Substances for Assessing the Risks of Nanomaterials. 2007 June 7; 1-68.
4. Organization for Economic Co-operation and Development (OECD) Guidelines for Testing of Chemicals: Section 4 Health Effects Guidelines.
5. Scientific Committee on Consumer Products Opinion on Safety of Nanomaterials in Cosmetic Products. 2007 Dec. 18; 1-63.
6. International Organization for Standardization, International Electrotechnical Commission, National Institute of Standards and Technology and OECD International Workshop on Documentary Standards for Measurement and Characterization for Nanotechnologies, Final Report, 2008 June; 1-40.
7. OECD Working Party on Manufactured Nanomaterials Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials, ENV/CHEM/NANO(2009)6/REV1, Environment Directorate Organization For Economic Co-Operation and Development Paris, 2009.
8. Scientific Committee on Consumer Safety Opinion Guidance on the Safety Assessment of Nanomaterials in Cosmetics. 2012 June. 26-27; 1-62.
9. ICCR (2011a) Currently Available Methods for Characterization of Nanomaterials,

ICCR Report of the Joint Regulator - Industry Ad Hoc Working Group, available at http://ec.europa.eu/consumers/sectors/cosmetics/files/pdf/iccr5_char_nano_en.pdf.

10. ICCR (2011b) Principles of Cosmetic Product Safety Assessment, A Report prepared for ICCR, available at http://ec.europa.eu/consumers/sectors/cosmetics/files/pdf/iccr5_safety_en.pdf.
11. Principles for Regulation and Oversight of Emerging Technologies, March 11, 2011, available at, http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/Principles-for-Regulation-and-Oversight-of-Emerging-Technologies-new.pdf.
12. Policy Principles for the U.S. Decision-Making Concerning Regulation and Oversight of Applications of Nanotechnology and Nanomaterials, June 9, 2011, available at, http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/nanotechnology-regulation-and-oversight-principles.pdf.
13. OECD Environment, Health and Safety Publications Series on the Safety of Manufactured Nanomaterials No. 27, List of Manufactured Nanomaterials and List of Endpoints for Phase One of the Sponsorship Programme for the Testing of Manufactured Nanomaterials: Revision 2010 December 1; 1-16.
14. Oberdorster, G., Maynard, A., Donaldson, K., Castranova, V., Fitzpatrick, J., Ausman, K., Carter, J., Karn, B., Kreyling, W., Lai, D., Olin, S., Monteiro-Riviere, N., Warheit, D., Yang, H; "Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy." *Particle and Fibre Toxicology***.** 2005; 2:8 (doi:10.1186/1743-8977-2-8).
15. Powers, K.W., Brown, S.C., Krishna, V.B., Wasdo, S.C., Moudgil, B.M., Roberts, S.M; "Research Strategies for Safety Evaluation of Nanomaterials. Part VI. Characterization of Nanoscale Particles for Toxicological Evaluation." *Toxicological Sciences*. 2006; 90 (2): 296-303.
16. FDA, 2010. Center for Drug Evaluation and Research MAPP. Office of Pharmaceutical Science. Reporting Format for Nanotechnology.
17. Rocks, S.S., Pollard, R.D., Levy, L., Harrison, P., and Handy, R. (2008), Comparison of risk assessment approaches for manufactured nanomaterials, Defra, London.
18. Chaudhry, Q., Bouwmeester, H. and Hertel, R.F. (2010) The Current Risk Assessment Paradigm in Relation to Regulation of Nanotechnologies, In. G.A. Hodge, D.M. Bowman and A.D. Maynard (eds), *International Handbook on Regulating Nanotechnologies*. Cheltenham: Edward Elgar, 124-143.
19. Cedervall T., Lynch I., Lindman S., Berggard T., Thulin E., Nilsson H., Dawson K.A., Linse S; "Understanding the nanoparticle-protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles." 2007: PNAS 104, 2050-2055.
20. Šimon, P. and Joner, E; "Conceivable interactions of biopersistent nanoparticles with food matrix and living systems following from their physicochemical properties." *Journal of Food and Nutrition Research*. 2008; 47, 51-59.
21. Lynch I. and Dawson K.A; "Protein- nanoparticle interactions." *Nano Today*. 2008; 3, 40–47.
22. Rouse, J.G., Yang, J., Ryman-Rasmussen, J.P., Barron, A.R., Monteiro-Riviere, N.A; "Effects of mechanical flexion on the penetration of fullerene amino acid-derivatized peptide nanoparticles through skin." *Nano Lett*. 2007; 7 (1):155-160.

23. Oberdorster, G; "Pulmonary effects of inhaled ultrafine particles." *Int Arch Occup Environ Health.* 2001; 74 (1):1-8.
24. Lockman P.R., et al. Nanoparticle surface charges alter blood-brain barrier integrity and permeability, *J. Drug Target.* 2004; 12(9-10): 635-641.
25. Geiser M., Kreyling W.G; "Deposition and biokinetics of inhaled nanoparticles." *Particle Fiber Toxicol*; 2010:7:2.
26. Larese, F.F., Agostin, F.D., Crosera, M., Adami, G., Renzi, N., Bovenzi, M., Maina, G; "Human skin penetration of silver nanoparticles through intact and damaged skin." *Toxicology* 2009; 255: 33-37.27.
27. Gratieri, T., Schaefer U.F., Jing L., Gao, M., Kostka, K.H., Lopez, R.F., Schneider, M. "Penetration of quantum dot particles through human skin." *J Biomed Nanotechnol,* 2010; 5: 586-595.
28. Sekkat, N., Guy, R.H; "Biological models to study skin permeation. Chapter in Pharmacokinetic Optimization in Drug Research." *Biological, Physiochemical and Computational Strategies*. 2001; 155-172.
29. OECD 428 Guidelines for the Testing of Chemicals: Skin Absorption: *In Vitro* Method.
30. Oberdorster, G., Oberdorster, E., Oberdorster, J; "Nanotechnology: An Emerging Discipline Evolving from Studies of Ultrafine Particles." *Environ Health Perspect***.** 2005b; 113 (7):823-839.
31. Eldridge, J.H., Hammond, C.J., Meulbroek, J.A., Staas, J.K., Gilley, R.M., Tice, T.R; "Controlled vaccine release in the gut-associated lymphoid tissues. I. Orally administered biodegradable microspheres target the peyer's patches." *J Control Release***.** 1990; 11: 205-214.
32. Shakweh, M., Besnard, M., Nicolas, V., Fattal, E; "Poly(lactide-co-glycolide) particles of different physiochemical properties and their uptake by Peyer's patches in mice." *Eur j Pharma Biopharma.* 2005; 61 (1-2):1-13.
33. CTFA (currently known as PCPC) Safety Evaluation Guidelines, 2007.
34. FDA – Redbook 2000. Toxicological Principles for the Safety Assessment of Food Ingredients. Updated July 2007.
35. U.S. Food and Drug Administration, "Guidance for Industry: Photosafety Testing," May 2003.
36. Landsiedel, R., Kapp, M.D., Schulz, M., Wiench, K., Oesch, F.; "Genotoxicity investigations on nanomaterials: methods, preparation and characterization of test materials, potential artifacts and limitations – Many questions, some answers" *Mutat Res.* 2009; 681: 241-258.
37. PCPC comments submitted in response to the FDA's Nanotechnology public meeting. September 2008.
38. Directive 2003/15/EC of The European Parliament and of the Council of 27 February 2003 amending Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products. Official Journal L66, 11/03/2003 p.26.
39. Teeguarden, J.G., Hinderliter, P.M., Orr, G., Thrall, B.D., Pounds, J.G.; "Particokinetics In Vitro: Dosimetry Considerations for In Vitro Nanoparticle Toxicity Assessments." *Toxicol Sciences.* 2007; 95(2): 300-312.