Guidance for Industry

Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act

DRAFT GUIDANCE

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For questions regarding this draft document, contact the Office of Science in the Center for Tobacco Products at 877-CTP-1373 or by e-mail at TobaccoIndustryQuestions@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Tobacco Products (CTP)

March 2012

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

The purpose of this guidance is to assist persons reporting to FDA the quantities of harmful and potentially harmful constituents (HPHCs) in tobacco products and tobacco smoke under section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 387d(a)(3)). In particular, at this time, while industry is developing laboratory capacity to comply with section 904(a)(3), FDA does not intend to enforce the statutory requirement to provide quantities of all constituents identified by FDA as HPHCs by June 22, 2012, if manufacturers or importers complete testing and reporting for an abbreviated list of HPHCs as set forth in this guidance. Specifically, this guidance document explains:

- The statutory requirement for testing and reporting quantities of HPHCs,
- What HPHCs will be the focus of FDA enforcement at this time,
- Who tests and reports quantities of HPHCs to FDA,
- When reports are submitted to FDA,
- What information is reported to FDA, and
- How reports should be submitted to FDA.

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

[1] This guidance has been prepared by the Office of Science in the Center for Tobacco Products (CTP) at FDA.

II. BACKGROUND

On June 22, 2009, the President signed the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Public Law 111-31) into law. The law grants FDA important new authority to regulate the manufacture, marketing, and distribution of tobacco products to protect the public health and to reduce tobacco use by minors. It also imposes certain obligations on industry, including reporting obligations. Among its many provisions, the Tobacco Control Act added section 904(a)(3) to the FD&C Act. This section requires each tobacco product manufacturer or importer, or an agent, to begin reporting to FDA on June 22, 2012, "all constituents, including smoke constituents, identified by [FDA] as harmful or potentially harmful to health in each tobacco product, and as applicable in the smoke of each tobacco product." Reports must be by brand[2] and by quantity in each brand and subbrand. For example, for a manufacturer using the brand name "Acme," separate reports need to be submitted for the subbrands "Acme 100s" and "Acme Kings." For tobacco products that were not on the market on the date that the Tobacco Control Act was enacted (June 22, 2009), section 904(c)(1) of the FD&C Act requires that these reports be submitted to FDA at least 90 days before the product is delivered for introduction into interstate commerce.

We have taken several steps to identify HPHCs to be reported under section 904(a)(3) of the FD&C Act. We issued a final guidance discussing our current thinking on the meaning of "harmful and potentially harmful constituent" in the context of implementing the HPHC list requirement.[3] In addition, on August 12, 2011, we issued a public notice in the *Federal Register* describing the criteria we had tentatively concluded we would use to assist the Agency in identifying HPHCs, listing 96 HPHCs we identified using those criteria, and asking the public and interested parties to submit relevant scientific and other information by October 11, 2011 (76 FR 50226). After reviewing comments received in response to this notice, and as directed by section 904(e) of the FD&C Act, we established the list of HPHCs and published it in the *Federal Register*.[4]

As described in this guidance, we do not intend, at this time, to enforce certain aspects of the requirements in section 904(a)(3) of the FD&C Act. However, we intend to move toward full implementation and enforcement of the statutory requirement to report quantities of all HPHCs on FDA's established list, as appropriate. We anticipate that this guidance will be revised or withdrawn as we do so. We intend to use the information submitted pursuant to sections 904(a)(3) and 904(c)(1) of the FD&C Act to meet the requirements of section 904(e) of the FD&C Act regarding a list of HPHCs in each tobacco product by brand and by quantity in each brand and subbrand. Also, the information will be used to comply with section 904(d)(1) of the FD&C Act, which requires FDA to publish a list of HPHCs, by brand and by quantity in each brand and subbrand, in a format that is understandable and not misleading to lay persons.

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[2] The term *brand* is defined in section 900(2) of the FD&C Act (21 U.S.C. 387(2)) as "a variety of tobacco product distinguished by the tobacco used, tar content, nicotine content, flavoring used, size, filtration, packaging, logo, registered trademark, brand name, identifiable pattern of colors, or any combination of such attributes."

[3] Available on the Internet at: http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm241339.htm.

[4] The established list is available on the Internet (under the Regulatory Information heading) at http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/default.htm.

In addition, section 915(a) of the FD&C Act (21 U.S.C. 387o(a)) requires FDA to issue regulations requiring testing and reporting of tobacco product constituents, ingredients, and additives, including smoke constituents, by brand and subbrand, that FDA determines should be tested to protect the public health. Section 915(a) of the FD&C Act calls for FDA to issue these regulations no later than April 1, 2013. Once regulations promulgated under section 915 of the FD&C Act become effective, section 904(a)(3) of the FD&C Act requires that a manufacturer, importer, or agent comply with these regulations in reporting HPHCs.

III. HPHCs TO BE REPORTED TO FDA

We recognize that industry will have a short time between the establishment of the HPHC list and June 22, 2012 when the reporting obligations under section 904(a)(3) are effective. We also recognize that manufacturers or importers (particularly small tobacco product manufacturers[5]) may not currently have the in-house laboratory capabilities to test for quantities of HPHCs. Consequently, manufacturers or importers may rely on contract laboratories for HPHC testing. Because this will be the first time that tobacco product manufacturers or importers are required to report quantities of HPHCs, contract laboratories may not be prepared for the large volume of requests for the testing of quantities of the HPHCs for all brands and subbrands of tobacco products marketed prior to June 22, 2012. In addition, some contract laboratories may not yet be able to test for each of the constituents on FDA's established list of HPHCs. However, we think that within the timeframes described in section V of this guidance, there will be adequate time for manufacturers or importers, including those relying on contract laboratories, to test and report on an abbreviated list of HPHCs. Therefore, we do not intend to enforce the requirements to test and report quantities of all HPHCs on FDA's established list if manufacturers or importers report, no later than the dates described in section V, quantitative information for the abbreviated list of HPHCs (Table 1).

[5] The definition of the term *small tobacco product manufacturer* is discussed in section V.B.

Table 1. Abbreviated List of Harmful and Potentially Harmful Constituents

HPHCs in Cigarette Smoke	HPHCs in Smokeless Tobacco	HPHCs in Roll-your-own Tobacco and Cigarette Filler[6]
Acetaldehyde	Acetaldehyde	Ammonia
Acrolein	Arsenic	Arsenic
Acrylonitrile	Benzo[a]pyrene	Cadmium
4-Aminobiphenyl	Cadmium	Nicotine (total)
1-Aminonaphthalene	Crotonaldehyde	NNK*
2-Aminonaphthalene	Formaldehyde	NNN**
Ammonia	Nicotine (total and free)	
Benzene	NNK*	
Benzo[a]pyrene	NNN**	
1,3-Butadiene		
Carbon monoxide		
Crotonaldehyde		
Formaldehyde		
Isoprene		
Nicotine (total)		
NNK*		
NNN**		
Toluene		

* 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

** N-nitrosonornicotine

We identified the HPHCs on this list after considering several factors. We selected constituents for which testing and analytic methods are well established and widely available. We also selected constituents that represent several different chemical classes (e.g., polyaromatic hydrocarbons, tobacco-specific nitrosamines, carbonyl compounds, aromatic amines, metals, and volatile organic compounds). These constitute a representative sample of the HPHCs on FDA's established HPHC list, providing a basis for beginning to study regulated tobacco products pending submission of information for all HPHCs on the established list. Finally, we selected a small number of constituents so that industry can begin testing and reporting, and FDA can begin analyzing HPHC information, in a relatively short time. We have identified HPHCs by product type because different product types may contain different HPHCs. For example, carbon monoxide is produced during combustion so it is included on the abbreviated list of HPHCs for cigarette smoke, but not included on the list for smokeless tobacco products, roll-your-own tobacco, or cigarette filler.

[6] *Roll-your-own tobacco* is defined in section 900(15) of the FD&C Act to mean "any tobacco product which, because of its appearance, type, packaging, or labeling, is suitable for use and likely to be offered to, or purchased by, consumers as tobacco for making cigarettes." The term *cigarette filler* is not defined in the FD&C Act. For purposes of this guidance, we intend *cigarette filler* to mean the cut, ground, powdered, or leaf tobacco that is a component of a cigarette.

IV. WHO SUBMITS 904(a)(3) REPORTS

Under section 904(a)(3) of the FD&C Act, "each tobacco product manufacturer or importer, or agents thereof" must report quantities of HPHCs for tobacco products by brand and subbrand. We interpret this to mean that domestic manufacturers, or their agents, are to submit the required HPHC information for products they manufacture. For imported tobacco products, the required HPHC information is to be submitted by either the foreign manufacturer or the importer, or an agent, of the product. The definition of *tobacco product* in section 201(rr)(1) of the FD&C Act includes "any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product)" (21 U.S.C. 321(rr)(1)). We therefore interpret section 904(a)(3) of the FD&C Act to cover any regulated tobacco product, whether for sale to consumers or for further manufacturing.[7] At this time, however, we intend to enforce the HPHC reporting requirements for finished tobacco products for consumer use in the following categories:

- Cigarettes (report HPHC quantities in smoke and filler)
- Smokeless tobacco (e.g., snus, snuff, plug, chew, loose leaf)
- Roll-your-own tobacco

At this time, we do not intend to enforce the requirement to report HPHCs under section 904(a)(3) against manufacturers and importers of other products (e.g., manufacturers of components sold to manufacturers or to consumers for incorporation into finished tobacco products for consumer use). We are not aware of established test methods to measure HPHCs in separated or unincorporated components of tobacco products other than cigarette filler and roll-your-own tobacco, and we also believe that testing finished products that are ready for consumer use without further assembly will provide information about the potential exposure of consumers and others, taking into account the effect of components and product design. If we find that additional information is needed to protect the public health, we may reconsider these enforcement policies.

This guidance does not apply to the testing and reporting of quantities of HPHCs for tobacco products that are not currently subject to Chapter IX of the FD&C Act (see section 901(b) of the FD&C Act (21 U.S.C. 387a(b))).

V. WHEN 904(a)(3) REPORTS ARE SUBMITTED TO FDA

Section 904(a)(3) of the FD&C Act requires the reporting of quantities of all HPHCs on FDA's established list, by brand and subbrand, beginning no later than June 22, 2012. As described in section III of this guidance, at this time we do not intend to enforce this requirement against manufacturers or importers of finished tobacco products provided that quantities of the HPHCs

[7] *See* the guidance for industry, *Listing of Ingredients in Tobacco Products*, available on the Internet at http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm191982.htm (explaining that the definition of tobacco product in the FD&C Act includes components, parts, and accessories of tobacco products, whether they are sold for further manufacturing or for consumer use).

identified in Table 1 are reported for all of their products, by brand and subbrand, no later than the dates identified in the following sections.

A. Products Marketed Prior to June 22, 2012: Tobacco Product Manufacturers That Are Not Small Tobacco Product Manufacturers

At this time, for a manufacturer or importer (or agents thereof), other than a small tobacco product manufacturer, we do not intend to enforce the requirement to test and report quantities of all HPHCs on FDA's established list if manufacturers or importers report quantities of the HPHCs identified in Table 1 for all of their products, by brand and subbrand, no later than September 22, 2012.

B. Products Marketed Prior to June 22, 2012: Small Tobacco Product Manufacturers

We recognize that small tobacco product manufacturers are unlikely to have their own laboratory facilities for the testing of HPHCs and are likely to be particularly reliant on contract laboratories that may have limited capacity at this time. Accordingly, at this time we do not intend to enforce the requirement for small tobacco product manufacturers to test and report quantities of all HPHCs on FDA's established list, provided that such a manufacturer report quantities of the HPHCs identified in Table 1, for all its products, by brand and subbrand, no later than December 22, 2012.[8] This additional 3months from the date that other manufacturers will report quantities of HPHCs should allow contract laboratories sufficient time to complete testing for HPHCs identified in Table 1 for both large and small tobacco product manufacturers and importers within the extended timeframes set forth in this guidance.

Section 900(16) of the FD&C Act defines a *small tobacco product manufacturer* as "a tobacco product manufacturer that employs fewer than 350 employees. For purposes of determining the number of employees of a manufacturer under the preceding sentence, the employees of a manufacturer are deemed to include the employees of each entity that controls, is controlled by, or is under common control with such manufacturer." [9] A small tobacco product manufacturer submitting 904(a)(3) information should certify on the eSubmitter or paper form (described in section VII) that it has fewer than 350 employees at the time of submission and should have documentation available for submission to FDA on request or for inspection to demonstrate that it meets the statutory definition of a small tobacco product manufacturer.

C. Products First Marketed On or After June 22, 2012

[8] Section 915 of the FD&C Act provides that regulations issued under its authority are to have separate compliance dates for small tobacco product manufacturers, providing additional time for initial compliance. Section 904(a)(3) of the FD&C Act does not contain similar provisions. In addition, section 915(f) of the FD&C Act explicitly states that these small tobacco product manufacturer provisions must not be construed to authorize the extension of any deadline or otherwise affect any timeframe under any other provision of the FD&C Act. Therefore, an extension in time to comply is not required by the FD&C Act.

[9] The definition of a *tobacco product manufacturer* in the FD&C Act includes any person "who imports a finished tobacco product for sale or distribution in the United States" (section 900(20) of the FD&C Act). Therefore, the 350 employee threshold applies to importers.

For a tobacco product that was not on the market on or after June 22, 2009, section 904(c)(1) of the FD&C Act requires all tobacco product manufacturers, regardless of their size, to submit HPHC quantities and other information at least 90 days prior to marketing the product. We do not intend, at this time, to enforce this requirement in section 904(c)(1) to test and report quantities of all HPHCs on FDA's established list for products not previously on the market, if a manufacturer or importer reports quantities for the HPHCs identified in Table 1 of this guidance at least 90 days prior to marketing the product in the United States.

It is important to remember that the section 904(c)(1) testing and reporting requirement is separate from the requirements that must be satisfied before you may market a new tobacco product (sections 905 and 910 of the FD&C Act (21 U.S.C. 387e and 387j)), or modified risk tobacco product (section 911 of the FD&C Act (21 U.S.C. 387k)). Depending on the nature of a new tobacco product or modified risk tobacco product, testing and reporting HPHCs on the list in Table 1 may not be adequate to meet the statutory standards for marketing authorization; quantities for additional HPHCs may be necessary. This guidance does not represent any intention to exercise enforcement discretion with respect to the statutory requirements for the marketing authorization of new tobacco products or modified risk tobacco products.

If the only change to your product after June 22, 2012, is a change to the product label or labeling that will not alter the quantities of HPHCs found in the tobacco product or its smoke, you do not need to conduct additional testing to comply with section 904(c)(1) of the FD&C Act. However, if changes to the product label or labeling include a product name change, then you must report the name change to FDA so that we may associate the quantities of HPHCs with the marketed product bearing that brand or subbrand name.

VI. WHAT INFORMATION IS TO BE REPORTED TO FDA

A. Manufacturer or Importer Identification

The name and address of each tobacco product manufacturer or importer, and the name and address of any agent reporting HPHCs on their behalf, are to be submitted along with HPHC information. FDA requests that you also provide information to assist us in communicating with you:

- Telephone and FAX numbers of the manufacturer or importer;
- FDA Establishment Identifier (FEI) number, if known;
- A Data Universal Numbering System (D-U-N-S) number for your headquarters, if you have one;
- Contact information for your point of contact including
    - Title, name, and mailing address;
    - E-mail address;
    - Telephone and FAX numbers.

The business entity identifier recognized by the FDA Data Council is the D-U-N-S number. Providing the site-specific D-U-N-S number for your headquarters will help prevent inaccuracies

in FDA's database. Dun & Bradstreet assigns and maintains a database of the D-U-N-S numbers, which serve as unique identifiers of business entities. Upon application, each business entity is assigned a distinct site-specific 9-digit D-U-N-S number. If the D-U-N-S number for a location has not been assigned, a business may obtain one for no cost directly from Dun & Bradstreet (http://www.dnb.com).

B. Tobacco Product Identification

Under section 904(a)(3), tobacco product manufacturers or importers are required to submit a listing of HPHCs for "each tobacco product by brand and by quantity in each brand and subbrand." Each product for which a listing of HPHCs is submitted is to be clearly and uniquely identified by its brand and subbrand, which includes identifying the type of tobacco product (i.e., cigarette, smokeless (e.g., snus), or roll-your-own tobacco), and any brand and subbrand names. Also, include the package size or sizes for each product brand and subbrand. If the package size will not affect quantities of HPHCs, you do not have to test each package size. FDA also recommends that a unique product identification number, such as a Universal Product Code, be included for each product to help the Agency track and file your submission, and communicate with you about your submission. In addition, we request that you provide the name, mailing address, telephone number, and FAX number for the testing laboratory or laboratories.

C. HPHC Quantities and Testing Information

Section 904(a)(3) of the FD&C Act requires the reporting of quantities of HPHCs in each tobacco product and as applicable in the smoke of each tobacco product. This information is intended to provide the Agency with information (1) to assist with implementation of the FD&C Act (e.g., developing tobacco product standards and making substantial equivalence determinations) and (2) to assist with the publication of a list of HPHCs by brand and subbrand that is useful for comparing HPHC levels in tobacco products. We therefore understand the statute to require that quantities must be reported in a manner that provides a basis for understanding levels of HPHCs in individual tobacco products or their smoke per unit of use, and for comparing relative quantities of HPHCs associated with different products or their smoke. Consequently, FDA interprets the term *quantity* to mean a unit of mass per unit of use (e.g., per cigarette or per pouch) or a unit of mass per mass of tobacco. For portioned tobacco products, you should report HPHC quantities per unit of use, and include a measurement of the mean mass with standard deviation of the mean. For non-portioned tobacco products, (e.g., a container of loose snuff or of roll-your-own tobacco), you should report HPHC quantities per gram of the product with standard deviation of the mean. For cigarette smoke, you should report HPHC quantities per cigarette. HPHC quantities and tobacco mass should be reported in terms of the International System of Units (e.g., grams, micrograms, nanograms, picograms, or milligrams), which provides a consistent, reliable system of measurement, and you should use at least three significant figures.[10]

[10] When reporting a quantity, you should round to the last appropriate significant figure. For example, if an HPHC quantity is determined to be 54.321 nanograms (ng)/cigarette and the measurement should be expressed as three significant figures, then the quantity should be rounded and reported as 54.3 ng/cigarette. It would not be appropriate to report the quantity as 50.0 ng/cigarette or 54.0 ng/cigarette.

Section 904(a)(3) is also intended to provide information that is representative of your product as marketed. Use a testing protocol to measure HPHCs in tobacco products or tobacco smoke that involves appropriate sampling techniques to select samples for testing, and provides reproducible results based on multiple measurements. In reporting quantities derived from such tests, we believe it is necessary to include a statement of average values and variability among these multiple measurements. Therefore, you are to report the mean mass and a measure of the variability among multiple measurements. We strongly recommend that you provide the standard deviation of the mean to report variability and that you report the number of replicate measurements made in determining the mean mass and standard deviation. For portioned products, you also are to include a statement of the mean mass of tobacco in each product and a measure of the variability among multiple measurements. We strongly recommend using standard deviation of the mean to describe the variability among measurements.

With respect to the requirement in section 904(a)(3) that manufacturers and importers report quantities of HPHCs "in the smoke of each tobacco product," we note that different smoking regimens (e.g., intense or non-intense)[11] are designed to collect different amounts of smoke from a given tobacco product for analysis and would be expected to provide a range of quantities of HPHC levels for the smoke of a given tobacco product. Therefore, we believe that information about the smoking regimen that was used to determine reported HPHC values is necessary for the interpretation and comparison of HPHC quantities reported, and you are to include this information in your report. FDA recommends that you also provide information on the smoking machine used to collect mainstream smoke (i.e., linear or rotary).

We recommend that the quantity of each HPHC in cigarette smoke be determined by both the non-intense and intense smoking regimens. The two smoking regimens are expected to provide the Agency with information about different deliveries of HPHCs possible for each tobacco product. FDA recommends seven replicates for the determination of quantities for all HPHCs, except nicotine and carbon monoxide in cigarette smoke. For nicotine and carbon monoxide in cigarette smoke, we recommend 20 replicates.

FDA also recommends that the following information be submitted for each HPHC, which will aid FDA in evaluating the data:

- Number of replicate measurements;
- Date (or date range) of testing;
- Date (or date range) when the tested product was manufactured; and
- Analytical methods used to extract, separate, and detect the HPHCs.

For smokeless tobacco products, FDA recommends that you use the CDC method to calculate free nicotine (74 FR 712, January 7, 2009).

VII. HOW 904(a)(3) REPORTS SHOULD BE SUBMITTED

[11] By intense smoking regimen we mean Canadian Intense, Health Canada Test Method T-401, and by non-intense smoking regimen we mean ISO 3308:2008 and ISO 5387:2000.

The FDA eSubmitter tool is an electronic application designed to streamline the data entry and submission process for reporting HPHCs. Users of the eSubmitter tool first download and install the computer application and then enter all data. To facilitate data entry in relevant sections, users can populate an Excel file and import data into eSubmitter. The tool alerts the user if there is missing information. The eSubmitter tool is available at http://www.fda.gov/ForIndustry/FDAeSubmitter.

Users of the eSubmitter tool can use the FDA Electronic Submissions Gateway (ESG) to securely submit their report to CTP and receive an automatic acknowledgement of FDA receipt. The FDA ESG is used across FDA as the portal for receipt of electronic regulatory submissions. The FDA ESG system requires users to apply for a free account before submitting data, a process which can take one to three weeks. FDA therefore urges the user to apply for ESG accounts well in advance of the deadline for data submission. Once approved, the user can send all submissions to CTP using the eSubmitter tool and FDA ESG. Instructions on obtaining an ESG account are available at http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm188949.htm.

Although electronic submission is not required, FDA strongly encourages electronic submission for efficient and timely data submission and management. If an electronic submission is not possible or practical, an alternative tool for paper submissions is available at www.fda.gov/tobaccoinfoindustry. If the ESG is not used, submissions can be mailed to:

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