



May 20, 2013

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-N-0227, Tobacco Product Manufacturing Practice

The undersigned organizations submit these comments in Docket No. FDA-2013-N-0227, in response to the notice published in the volume 78 of the Federal Register on March 19, 2013 (78 F.R. 16824-25). This notice provides interested parties the opportunity to submit comments on recommendations for “current good manufacturing practices” (“GMPs”) for tobacco products submitted to FDA by 13 tobacco companies on January 10, 2012 (“tobacco company proposal”).

Section 906(e) of the Food, Drug and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act of 2009 (“The Act”), requires the Secretary to prescribe regulations “... requiring that the methods used in, and the facilities used for, the manufacture, preproduction design validation (including a process to assess the performance of a tobacco product), packing, and storage of a tobacco product conform to current good manufacturing practice, or hazard analysis and critical control point methodology. . . to ensure that the public health is protected and that the tobacco product is in compliance with [the provisions of the Act].”

Summary of Major Points

1. FDA should itself set standards for manufacturing practices and should not delegate this function to tobacco product manufacturers.
2. Any regulation of manufacturing practices must require consistency in the content of harmful constituents in tobacco products on a brand-by-brand and batch-by-batch basis. The current practice has not even attempted to provide such consistency and consequently has exposed consumers to unnecessary risk. Rather than attempting to achieve consistency in risk exposure, manufacturers have instead sought to achieve consistency in sensory appeal.
3. Any regulation of manufacturing practices must eliminate intrabrand batch-to-batch inconsistencies in the content of harmful constituents, including constituents that occur naturally in tobacco, constituents that are the result of blending changes, and constituents that occur as a result of the addition of additives, changes in product design, or changes in product blend and must include strict product testing requirements.

Discussion

A. FDA should itself establish minimum requirements for manufacturing practices and should not delegate this function to tobacco product manufacturers. The thirteen tobacco companies that submitted the proposed regulations apparently did so on their own initiative and not at the instance of FDA. The companies propose, in essence, that FDA abdicate its responsibility to develop standards of “good manufacturing practice” and instead delegate this aspect of its regulatory authority to the regulated companies themselves. Given the Congressional findings underlying the Act, it would be wholly inappropriate for FDA to permit the companies that created and that perpetuated the largest public health disaster in American history to exempt themselves from regulation in this manner.¹

The tobacco company proposal misstates the purposes of the regulatory policy and, if adopted, would perpetuate many of the practices that created the public health crisis the Act was designed to address. Moreover, the proposal falls far short of GMPs that are applicable to other product categories regulated by FDA.

The concept of GMPs for a product that, used as intended by the manufacturer, kills half of its users, is self-contradictory. No manufacturing practice that results in so dangerous a product should be characterized as “good,” and FDA should not place its imprimatur on such practices with such a characterization. FDA should use its authority under Section 906(e) to establish minimum criteria for manufacturing practices along the lines suggested in these comments.

The statute requires that regulations under section 906(e) apply, inter alia, to “preproduction design validation (including a process to assess the performance of tobacco products).” Accordingly, in order to develop such regulations, FDA should carefully examine the processes for preproduction design validation and assessment of the performance of tobacco products that have traditionally been utilized in the tobacco industry. Such an analysis will produce the following conclusions:

1. The major tobacco companies’ process for preproduction design is remarkably sophisticated and finely tuned and takes account of a multitude of considerations.
2. The purpose of this process is to design products that will provide the most satisfactory sensory experience for the intended user. Product design is used to develop products targeted to appeal to specific categories of intended users, including “young adults.”
3. Product design encompasses tobacco blending, use of additives to affect the sensory experience of the users, consideration of all other physical attributes of the product, including the paper, the filter, the packing, the way the cigarette is likely to be used (i.e., the likely number of puffs and puff intensity) and the delivery of nicotine.

¹ The decision of the United States District Court for the District of Columbia in *U.S. v. Philip Morris*, 449 F. Supp. 2d 1 (D.D.C. 2006), *aff’d in relevant part*, 955 F. 2d 1095 (D.C. Cir. 2009), *cert. denied*, 130 S. Ct. 3501(2010), recounts in exhaustive detail the conduct of the major participants in the tobacco industry over the course of more than 50 years and stands as an eloquent demonstration of why the sort of self-regulation the companies now propose is preposterous.

4. Production controls exist to ensure that the product actually manufactured conforms to the product design.

5. In the manufacture and design of tobacco products, maximization of sensory appeal is the pre-eminent consideration and takes precedence over other criteria.

6. The design and manufacture of products intended to maximize sensory appeal to users is not compatible with the design and manufacture of products intended to minimize the exposure of users to harmful constituents or to minimize the disease risk of users and is not appropriate for the protection of the public health as that term is used in the Act.

7. FDA should not promulgate or express approval of any process of product design or production control that does not have as its principal criterion minimizing the exposure of users to harmful constituents, minimizing the disease risk of users, and protecting the public health.

8. FDA should not promulgate or express approval of any process of product design or production control that does not expressly apply to components intentionally included in tobacco products by manufacturers.

These conclusions make it evident that the tobacco product manufacturers have totally failed to develop manufacturing practices designed to minimize the dangers to the public health caused by their products. Instead, they have devoted massive resources to creating manufacturing and design practices intended to maximize the sensory appeal of their products, encourage initiation, and discourage cessation—objectives that are precisely the opposite of the statutory purposes of the Tobacco Control Act. Tobacco product manufacturers therefore cannot be trusted to develop and institute manufacturing practices that meet the requirements of Section 906(e).

B. FDA should reject this attempt by tobacco product manufacturers to exclude from the concept of GMP anything that really could have a meaningful effect on public health.

The manufacturers argue that because tobacco products are inherently unsafe, GMPs for tobacco products, unlike GMPs for drugs, medical devices, and dietary supplements, “are not meant to assure the safety and effectiveness of a tobacco product.”² They argue that the purpose of GMPs for tobacco products is “to assure that the public health is protected and that the tobacco product is manufactured in compliance with the Act.”³ The measures they advocate, however, are inconsistent with the achievement of this objective.

According to the manufacturers, GMPs for tobacco products should be limited to three functions: “(1) to protect public health by providing assurance that tobacco products are not contaminated (prohibiting the introduction of substances in the tobacco products that present a risk of injury beyond that generally posed by the same category of tobacco product); (2) to prevent misbranded products; and (3) to allow tobacco product manufacturers the flexibility to

² Attachment 2: Preamble for Proposed Tobacco Product GMP Regulation. Docket No. FDA-2013-N-0227. Received by CTP/DDC 1/10/12 at 2.

³ *Id.*

manufacture, label, pack, and store tobacco products for different categories of tobacco products, different manufacturing processes, and the inherent variability of tobacco, while assuring all such activities are conducted in a controlled manner.”⁴

The manufacturers argue that because all tobacco products have “inherent risks,” GMPs “should not require tobacco product manufacturers to address those risks in this context.”⁵ However, the manufacturers nowhere explain why this should be the case. The fact that tobacco products have inherent risks should not prevent FDA, through GMPs, from ensuring that manufacturing processes designed to achieve different objectives (i.e., maximizing sensory appeal) do not thereby increase such risks. Processes that increase such risks would be directly contrary to the express goal of the Tobacco Control Act: to protect the public health.

The constricted scope and purpose of GMPs proposed by the manufacturers would constitute a radical and wholly unjustified departure from the scope and purpose of any GMPs ever considered or approved by FDA. The manufacturers argue that because tobacco products cannot be made wholly safe, they should be under no obligation to adopt manufacturing processes designed to minimize the risks posed by such products. The manufacturers argue that the scope of GMPs should be limited to minimizing contaminants that the manufacturers do not intend to include in such products. They argue that the *intentional* inclusion of hazardous components should not be covered by GMPs. According to the manufacturers, “a substance becomes a ‘contaminant’ only when it has been added to a tobacco product, *is not intended to be in the tobacco product*, and presents a risk beyond that generally posed by the same category of tobacco products.”⁶ In other words, they maintain that GMPs should not require manufacturers to avoid intentional actions that make the product more lethal or more addictive. There is, however, no logical reason why the fact that tobacco products cannot be made risk-free should lead to a policy that exempts manufacturers from a requirement to make them as safe as possible.

The manufacturers’ formulation of the proper objectives of GMPs is twisted and wholly unjustifiable. It should never be a good manufacturing practice to manufacture a product that could be made less hazardous. This is true regardless of whether the source of the potentially increased hazard is a contaminant that is introduced into the product unintentionally or a component that is introduced into the product intentionally. The proposed exemption for components intentionally introduced into the product cannot be justified. The fact that manufacturers would seek an exemption that would characterize as “good manufacturing practice” a process that fails to require them to reduce the hazards posed by their products to the minimum attainable level is shocking. The fact that manufacturers would seek an exemption that would characterize as “good manufacturing practice” a process that permits them intentionally to introduce components that make the product more hazardous is even more shocking.

⁴ *Id.*

⁵ *Id.* at 3.

⁶ *Id.* at 4 (emphasis supplied).

C. The alleged “inherent variability of tobacco products” is no excuse for not mandating manufacturing practices that would require the level of harmful constituents to be consistent on a batch-to-batch basis.

Manufacturers argue that because tobacco is an agricultural product with natural variations that result in different tastes, tobacco product manufacturers are required to combine such products in order to “produce a distinctive ‘blend’ that is primarily responsible for giving each tobacco product its distinctive sensory characteristics.”⁷ The manufacturers describe this process as “a combination of science and art to (1) achieve a tobacco blend that delivers a distinctive adult [sic] tobacco product consumer experience and (2) adjust the blend to maintain consistency of that tobacco product to account for natural tobacco variability.”⁸

It is true that tobacco companies do use such a process to produce their products and that the objective of the process is to produce a product with “distinctive sensory characteristics.” In fact, tobacco companies have achieved an incredible level of sophistication in achieving such “distinctive sensory characteristics.”⁹ This process is known as “product design” and tobacco manufacturers have spent billions of dollars perfecting product design in order to ensure that their products do in fact deliver the sensory characteristics that will appeal to particular markets.

There are several elements in product design. First, there is the blend of tobacco used. The manufacturers correctly state that each type of tobacco has its own particular taste and that different combinations will produce different tastes. It is also true, however, that each type of tobacco may contain different levels of toxicants and certain blends may contain far higher levels of toxicants than others.¹⁰ Second, manufacturers introduce additives into their cigarettes and have identified some 600 additives that are added to the tobacco in cigarettes.¹¹ The primary purpose of many of these additives is to influence the sensory characteristics of the cigarette,¹² and many such additives do so without imparting a “characterizing flavor.” For example, certain additives are used to mask the harsh flavor of nicotine, to produce a smooth taste sensation, or to improve the aroma of the smoke.¹³ These characteristics often appeal to target audiences, such as the “young adult market” and women.^{14,15} In addition, some additives promote the enhanced

⁷ *Id.* at 3.

⁸ *Id.*

⁹ Gordon, DL. Brown & Williamson Tobacco Corporations Research and Development Department. PM’s Global Strategy: Marlboro Product Technology. Aug. 26, 1992. Bates Nos. 620943165-216. No better demonstration of the sophistication of these efforts exists than this memorandum, created by Brown & Williamson’s research department, which attempts to use “reverse engineering” to deconstruct the product design of Marlboros marketed in the United States and throughout the world in order to identify those elements of the design that have accounted for Marlboro’s success. The memorandum purports to assess and describe “the product technology deemed critical to the Marlboro character in which “technologies such as tobacco selection, processing and cigarette design are used as flexible parameters to adapt for the primary technologies. The memorandum identifies numerous sophisticated processes as contributing to the distinctive sensory profile of Marlboro, including leaf/blend, blend components, cigarette construction, physical qualify, processing, casing/flavor, and sensory at 620943171.

¹⁰ Hoffman D, Hoffman I. The changing cigarette: 1950-1995: *J Toxicol Environ Health*. 1997;50:307-64 at 329-335.

¹¹ Rabinoff M, Caskey N, Rissling A, Park C. Pharmacological and chemical effects of cigarette additives. *Am J Public Health*. 2007;97:1981-91 at 1981.

¹² *Id.*

¹³ *Id.* at 1987.

¹⁴ Wayne GF, Connolly GN. How cigarette design can affect youth initiation into smoking: Camel cigarettes 1983-93. *Tob Control*. 2002;11:132-9 at i34-37.

delivery of nicotine to the smoker.¹⁶ Finally, manufacturers use product design to manipulate physical features of the cigarette to influence the sensory characteristics of the cigarette.¹⁷ For example, length, size, texture, color, and filter characteristics all impact the smoking experience.¹⁸

In their attempts to improve the sensory experience of cigarette smoking, the tobacco industry often uses additives and design features that increase toxicity. For example, when some additives are combusted they produce carcinogenic substances.¹⁹ In addition, by putting ventilation holes in the filter, manufacturers can influence the topography of smoking in manners that may increase its harmful effects.^{20,21}

We understand that the issue of additives implicates not only GMPs but also tobacco product standards. Section 907 of the FDCA gives the Secretary of HHS, through FDA, authority to promulgate new tobacco product standards in addition to those already in the statute. We urge FDA, separate from any action on GMPs, to use that authority to adopt rigorous product standards for tobacco products that will minimize the risks of these products and ensure that they contain minimal levels of harmful substances. Effective product regulation will make use of all relevant statutory authorities, including both Section 907 and Section 906(e).

D. GMPs for tobacco products should not permit manufacturers to ensure the consistent sensory appeal of tobacco products without also ensuring a consistent risk profile for these products.

The principal purpose of all the changes described above is to produce a distinctive sensory experience and, frequently, to produce a sensory experience that is deemed likely to appeal to a target segment of the market.^{22, 23, 24} Moreover, many such changes in sensory experience do not require changes in characterizing flavors.²⁵ Manufacturers assert that in order

¹⁵ Carpenter CM, Wayne GF, Connolly GN. Designing cigarettes for women: new findings from the tobacco industry documents. *Addiction*. 2005;100:837-51 at 839.

¹⁶ Rabinoff, *supra*, note 11 at 1982.

¹⁷ Carpenter, *supra*, note 15 at 842.

¹⁸ *Id.* at 842-845.

¹⁹ Martin LA, Byrd SK, Milofsky RE. Rapid communication: effects of tobacco processing on the quantity of benzo[a]pyrene in mainstream smoke. *J Toxicol Environ Health A*. 2003;66:1283-6.

²⁰ Strasser AA, Ashare RL, Kozlowski LT, Pickworth WB. The effect of filter vent blocking and smoking topography on carbon monoxide levels in smokers. *Pharmacol Biochem Behav*. 2005;82:320-9.

²¹ Burns D, Anderson C, and Gray N. Has the lung cancer risk from smoking increased over the last fifty years? *Cancer Causes Control*. 2011;22:389-97 at 396.

²² Carpenter, CM et al. New Cigarette Brands with Flavors that Appeal to Youth: Youth Marketing Strategies. *Health Affairs*. 2005;24:1601-1610. The article cites numerous instances of manufacturers discussing the appeal given taste sensations will have to the “young adult” market at 1603-05.

²³ Wayne, *supra*, note 14.. Quoting an industry document describing a chocolate/vanillin/licorice tobacco enhancer as “one of the most exciting and promising flavorants developed during the last several years. . .[with] significant appeal among the 18-24 year old smoker group. . .[that] is obviously the group we desperately are after.” at i35.

²⁴ Carpenter, *supra*, note 15.

²⁵ Panzano VC, et al. Human electroencephalography and the tobacco industry: a review of internal documents. *Tobacco Control*. 2010;19:153-159. Authors quote an industry scientist as concluding, “Our techniques are capable of detecting differences that are not apparent using normal subjective evaluations. Although subjectively undetectable, these differences most likely affect consumer acceptability and preference.” at 154.

to produce a sensory experience that is distinctive to a brand they may need to alter the blend of tobacco in a cigarette, manipulate additives, and change design features. Manufacturers have spent billions of dollars studying precisely how to produce a given sensory effect, how to make that sensory effect consistent over time, or how to alter the sensory effect of a brand over time to keep pace with changing consumer tastes.²⁶ The manufacturing process necessary to produce such a finely honed set of products is indeed a sophisticated one.²⁷ An internal Philip Morris memorandum described plans for “installing a sensory laboratory that allows the characterization of sensory effects of known and new compounds of interest (COI) on sensory systems within the upper and lower respiratory tract and mouth (RT&M).”²⁸

A memorandum from Brown & Williamson describes B&W’s attempt to use reverse engineering to identify the elements that characterize the Marlboro brand and its account aptly documents this sophistication. B&W’s analysis of Marlboro concludes,

It has long been known that PM [Phillip Morris] uses phosphates, ammonia, and/or diammonium phosphate (DAP) to alter blend chemistry. The role of these compounds in influencing many aspects of the blend and smoke chemistry has been well documented. And these compounds (and their impact on tobacco and smoke chemistry) contribute significantly to Marlboro’s sensory character.

Ammonia and/or phosphate. . .alter blend and smoke chemistry in order to reduce irritation. . ., enhance nicotine availability[, impart unique base flavor notes. . ., and enhance flavor compounds. . .].²⁹

In producing these precisely designed tobacco products, manufacturers have been utterly unconcerned with their health effects. Although tobacco product manufacturers have invested billions of dollars testing and retesting the sensory impact of design changes, they have been—and they remain-- indifferent to the effects such design changes may have on the harmfulness of their products. Manufacturers assert that “good manufacturing practices” are limited to practices that concern the avoidance of unintended contaminants in their products.³⁰ However, no such definition of GMPs has ever been adopted by FDA for any other product and no such definition should ever be acceptable for any product. Even for a product that inherently cannot be made

²⁶ Wayne GF, Connolly GN, Henningfield JE. Assessing internal tobacco industry knowledge of the neurobiology of tobacco dependence. *Nicotine Tob Res.* 2004;6:927-40. “Overall, it appears that enormous effort and resources were directed within the tobacco industry to assess the effects of tobacco on the smoker, as well as to determine product differences, and to apply these findings to product development.” at 930.

²⁷ Gordon, *supra*, note 9. Contains comparative information on numerous measures, such as “dry density,” filter pressure drop, filter efficiency, and paper porosity.” at 620943 196. It also offers data on cigarette deliveries, including ventilation, tar, nicotine, tar per puff, nicotine per puff, ratio of tar to nicotine, and number of puffs.

²⁸ Philip Morris. WSA 2002 Proposed Project Plan. 1 Mar 2002. Philip Morris. <http://legacy.library.ucsf.edu/tid/yrv94c00/pdf?search=%222085797245%22>. According to the memorandum, “the new laboratory shall enable us to measure threshold concentrations, suprathreshold dose-reponse functions, relative olfactory/gustatory versus somatosensory (trigeminal activity), hedonic ratings and their relation to stimulus concentrations, qualitative descriptors, time courses of quality and intensity (adaptation, habituation, change in relation of qualitative and/or hedonic descriptors over time of exposure, evoked potentials, localization of brain activity, and other Psychophysiological endpoints (e.g., ECG).”

²⁹ Gordon, *supra*, note 9, at 620943181-182. The memorandum also concludes that Philip Morris adds cocoa, liquorice, and propylene glycol in its processing of cigarettes at 690943192.

³⁰ Attachment 2, *supra*, note 2 at 3.

safe, no manufacturing practice can be a “good manufacturing practice” unless it ensures that the product is no more harmful than it has to be. GMPs should also require consideration not only of contaminants not intended to be part of the product, but also, and most importantly, of components of the product that the manufacturer intentionally included: the tobacco blend, the additives, and the other design elements.

Blending is done to achieve specific pH levels, taste, burning characteristics, and nicotine content and the type of tobacco blend significantly affects the pH level, nicotine content and toxicity of the smoke.³¹ Manufacturers maintain that they need to routinely adjust their tobacco blends to compensate for natural variations in different types of tobacco to maintain the “consistency” of their product. Their concept of “consistency,” however is a narrow one. By “consistency” they mean consistency of overall sensory experience to the customer. They are entirely indifferent to the need to maintain consistency of the health effects of their product. Thus, for example, in order to preserve consistency of sensory experience, manufacturers can and do change the blend of tobaccos in a way that may increase the tobacco-specific nitrosamine (TSNA) content of their cigarettes.³² Such a change can have a profound impact on the level of carcinogens the user is exposed to. There is no reason why the maintenance of consistent sensory experience—a purely commercial concern—should outweigh the public health consequences of changes that increase a user’s exposure to harmful constituents. No such change would be tolerated in food, drugs, or medical devices.³³ No such change should be tolerated for tobacco products.

FDA has *never* adopted GMPs that allow manufacturers to *intentionally* make a product less safe. Indeed, the very notion of “consistency” that the manufacturers champion is routinely included in GMPs as a means of ensuring that products from one batch to another are equally safe. The fact that the baseline level of safety is lower for tobacco products than for other products does not mean that the companies that design and manufacture tobacco products therefore should have license to make the product as unsafe as they please in order to maintain consistency of sensory experience. Put another way, even for a product that is inherently unsafe, no manufacturing practice should be validated by FDA unless it minimizes the public health risks presented by the product. No manufacturing process that places a higher priority on the maintenance of consistent sensory experience over the maintenance of consistent levels of health risk should be deemed to be a “good manufacturing practice.” Thus, “good manufacturing practices” must include consideration of all the elements the manufacturer intentionally puts in its product—not just the avoidance of elements that are not intended to be included.

Consideration of tobacco-specific nitrosamines presents a case in point. It is widely recognized that TSNAs are among the most virulent carcinogens in cigarettes.^{34,35,36} The nitrate

³¹ World Health Organization, International Agency for Research on Cancer (“IARC”) Monograph 83, Tobacco Smoke and Involuntary Smoking (2004) at 58.

³² Hoffmann D, Hoffmann I. The Changing Cigarette: Chemical Studies and Bioassays. Bethesda, Maryland: US Department of Health and Human Services, National Institutes of Health, National Cancer Center. 2001:159-91 at 172-173.

³³ It is inconceivable that a producer of a food product would argue that it should be permitted to change its product design to make a food taste better if the effect of the change were to increase the public’s exposure to a carcinogen.

³⁴ Ashley DL, Burns D, Djordjevic M, Dybing E, et al. The scientific basis of tobacco product regulation. *World Health Organ Tech Rep Ser.* TobReg. 2008;(951):1-277 at 54.

content of the tobacco blend (a precursor of TSNAs) influences the carcinogenic potential of the tobacco smoke.³⁷ Moreover, the level of TSNAs in smoke is largely determined by the preformed level of TSNAs in the rod.³⁸ Most of the TSNA is formed during the curing process.³⁹ It is also true that levels of TSNA can be nearly eliminated, either through changes in the curing process, or in the blend of tobacco chosen for a cigarette.⁴⁰ In recognition of the importance of reducing TSNA levels in cigarettes, by the late 1999 both R.J. Reynolds and Philip Morris announced plans to begin using low-TSNA tobacco in cigarettes.⁴¹ However, a 2010 study covering cigarettes manufactured by R.J. Reynolds, Philip Morris and Lorillard concluded that nitrosamine levels in U.S. cigarettes in 2010 were no lower than that had prevailed thirty years before.⁴² According to the authors of that study, “TSNA levels in the recently introduced new varieties of existing cigarette brands reflect a remarkable lack of any attempt to reduce, or at least control, the level of these carcinogens.”⁴³

Other studies also show that, in spite of the potential for reductions in TSNA levels, the level of TSNAs in domestic cigarettes has increased over time⁴⁴ and the large majority of cigarettes sold in the United States have a far higher TSNA content than cigarettes sold in other countries.⁴⁵ Perhaps not coincidentally, recently published research concludes that the lung cancer risks from smoking may be increasing in the United States due to cigarette design, and especially due to changes in smoking topography induced by ventilation holes in cigarette filters and increases in the levels of TSNAs in domestic cigarettes.⁴⁶ It appears that domestic cigarette manufacturers place a priority on preserving a consistent sensory experience even if the consistent sensory experience is produced by increasing the TSNA content of cigarettes.

Throughout the history of the tobacco industry, manufacturers have prioritized the maintenance of consistent sensory experience and ignored maintenance or minimization of consistent levels of risk. The so-called “good manufacturing practices” urged by the manufacturers would perpetuate these misguided priorities.

³⁵ Hoffman D, Rivenson A, Hecht SS. The biological significance of tobacco-specific N-Nitrosamines: smoking and adenocarcinoma of the lung. *Crit. Reviews in Toxicology*. 1996; 26:199-211 at 202-206. Biomarkers of TSNAs in the urine predict the risk of lung cancer in smokers even after controlling for the intensity and duration of smoking.

³⁶ Burns D, Anderson C, Gray N. Do changes in cigarette design influence the rise of adenocarcinoma of the lung? *Cancer Causes Control*. 2011;22:13-22 at 20.

³⁷ WHO, *supra*, note 31 at 58.

³⁸ Stepanov I, Knezevich A, Zhang L, Watson C, Hatsukami D, Hecht SS. Carcinogenic tobacco-specific, N-nitrosamines in US cigarettes: three decades of remarkable neglect by the tobacco industry. *Tobacco Control*. 2012;21:44-48.

³⁹ WHO, *supra*, note 31 at 64-65.

⁴⁰ *Id.* at 44. Ashley, *supra*, note 34 at 47-48, 54. There are numerous technologies available for greatly reducing the nitrosamine levels in cigarette tobacco. *See, e.g.*, Star Scientific Corporation, Form 10-K for 2001 at 3, March 29, 2002. Ashley DL, Beeson MD, Johnson DR, *et al.* Tobacco specific nitrosamines in tobacco from U.S.-brand and non-U.S. brand cigarettes. *Nicotine Tob Res*. 2003;5:323-331. WHO, *supra*, note 31 at 65 and sources cited therein.

⁴¹ Stepanov, *supra*, note 38 at 45, n. 16-18.

⁴² *Id.* at 48.

⁴³ *Id.*

⁴⁴ Hoffman, *supra*, note 32 at 307.

⁴⁵ Ashley, *supra*, note 34, at 55-57; WHO, *supra* note 31, at 62-64.

⁴⁶ Burns, *supra*, note 21.

E. FDA’s guidance for industry on demonstrating substantial equivalence for tobacco products provides no support for the positions advocated by the manufacturers.

The manufacturers argue that a statement made by FDA in its guidance for industry on demonstrating substantial equivalence for tobacco products is somehow relevant to the establishment of good manufacturing practices. In that guidance FDA stated, “[A]t this time, FDA does not intend to enforce the requirements of sections 910 and 905(j) for tobacco blending changes required to address the natural variation of tobacco (e.g., blending changes due to variation in growing conditions) in order to maintain a consistent product.”⁴⁷ The manufacturers argue that this statement is an acknowledgment that adjustments in tobacco blends are “required...in order to maintain a consistent product.”⁴⁸ It is not clear, however, that FDA meant to confine the definition of “a consistent product” to consistency in sensory characteristics. A changed tobacco blend may be intended to produce consistency in sensory characteristics, but if that change comes at the expense of an increase in TSNA content, for example, it would be perverse to consider the new product to be “consistent” with the predicate product. “Consistency” must refer not only to consistency of sensory experience, but also to consistency in risk profile.

The manufacturers also argue that FDA “has . . . acknowledged that such adjustments to the tobacco blend are not “intended to alter the chemical or perception properties of a tobacco product.”⁴⁹ FDA’s statement will not bear this characterization, however. FDA acknowledges that some changes in tobacco blend, i.e., those that do not alter the *chemical or perception* properties, of a tobacco product, may be characterized as “maintaining a consistent product.” However, FDA’s statement makes it clear that changes in a tobacco blend that do alter *either the chemical or the perception properties* of a product are not within the scope of changes that do not require reporting under Section 905j. Blending changes that increase the level of carcinogens do alter the chemical properties of a product. Nothing FDA has said is to the contrary and the industry’s interpretation of the language FDA used in its guidance is a crude distortion of that language.

Moreover, whatever the status of blending changes under Section 905j, no change in blending that increases the risk exposure presented by a tobacco product should qualify as a good manufacturing practice. Such changes are harmful to the public health. Moreover, such changes are even more pernicious to the public health if they simultaneously increase the risk exposure presented by the product while maintaining consistency of sensory experience. Neither in the context of substantial equivalence nor in the context of GMPs should manufacturers be permitted to make product changes that maintain sensory consistency without the maintenance of exposure risk consistency. The need to maintain a given sensory experience for consumers is not an acceptable excuse for manufacturing and selling a product that contains harmful and potentially harmful constituents in quantities that could be reduced or eliminated. No practice—whether it be blending, use of additives, or changes in product design— should be deemed to be good manufacturing practice unless such practice requires the use of measures designed to reduce the health consequences of tobacco use to the greatest possible degree.

⁴⁷ Guidance for Industry and FDA Staff, Section 905j Reports: Demonstrating Substantial Equivalence for Tobacco Products. Jan. 5, 2011 at 4.

⁴⁸ Attachment 2, *supra*, note 2 at 3.

⁴⁹ *Id.*

F. It is not an acceptable manufacturing practice to manufacture products without having an effective means to measure harmful constituents.

Manufacturers have made contradictory arguments regarding the measures they take to avoid increasing the risk exposure presented by their products. On the one hand, they have argued that they maintain strict quality control measures⁵⁰ but on the other they argue that they cannot even consistently measure the quantity of many significant toxicants and carcinogens in their product.⁵¹ If the level of such constituents cannot be measured accurately, it is irresponsible for manufacturers to make changes in their product that may increase the levels of such constituents. In fact, the means of measuring harmful constituents is far more consistent and reliable than suggested by the industry. One of the major shortcomings of the GMPs suggested by the industry is the absence of criteria for product testing for harmful constituents that would ensure that such testing is consistent, at a minimum, with standards to be promulgated by FDA.

G. Manufacturing regulations should ensure consistency within a batch or lot.

The proposed GMPs define “batch or lot” so loosely that the concept lacks effective meaning. According to the preamble, a “batch or lot” can mean anything a manufacturer wants it to mean so long as the product manufactured within such batch or lot is “intended to meet the same specifications.”⁵² FDA has *never* adopted GMPs that allow manufacturers to *intentionally* make a product less safe. Indeed, the very notion of “consistency” that the manufacturers champion is routinely included in GMPs as a means of ensuring that products from one batch to another are equally safe. The fact that the baseline is lower for tobacco products does not mean that the companies therefore have license to make the product as unsafe as they wish in order to maintain consistency of sensory experience. Put another way, even for a product that is inherently unsafe, no manufacturing practice can be a “good manufacturing practice” unless it ensures that the product is not made to be even less safe. Under such a definition, there is no requirement for products within a batch or lot actually to meet the same specifications. In order for the concept to have any effective meaning, there should be a requirement for the product not to exceed well-defined harmful constituent levels within a batch or lot.

H. Manufacturing regulations should ensure conformance to specifications.

The proposed GMPs require manufacturers to “develop, conduct, control, and monitor manufacturing processes to ensure that tobacco products conform to your specifications” and to establish and maintain adequate process control to ensure conformance to specifications.⁵³ However, the definition of “specifications” is so vague as to be meaningless. Under the industry proposed GMPs, specifications cover only those criteria each manufacturer designates and by leaving out specifications for harmful constituents a manufacturer could render such specifications useless for the protection of public health. Thus, a set of specifications could and

⁵⁰ R.J. Reynolds Comments on FDA Proposed Rule: Tobacco Products-Exemptions From Substantial Equivalence Requirements. Docket No. FDA-2010-N-0646-0009 at 12-14.

⁵¹ Comments of R.J. Reynolds submission to FDA-2012-D-0049-Request for Comments on “Draft 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” at 5.

⁵² Attachment 2, *supra*, note 2 at 4.

⁵³ Attachment 1: Proposed Tobacco Product GMP Regulation. Docket No. FDA-2013-N-0227. Received by CTP/DDC 1/10/12, at 10, Subpart H.

likely would ignore all aspects of a tobacco product relevant to the public health. Moreover, the proposed regulations explicitly state that “in-process or finished tobacco product testing is not required” unless the manufacturer itself determines that testing is a necessary process control.⁵⁴ Specifications without testing are meaningless. It is clear that conformance to specifications is intended to serve the commercial interests of the manufacturers, not to protect the health of consumers. Specifications are meaningful only if they include all elements of a tobacco product that can adversely affect the health of consumers. Failure to establish and enforce such specifications is inconsistent with good manufacturing practice.

I. Regulations concerning manufacturing should require manufacture and process controls.

The GMPs are devoid of meaningful content regarding manufacture and process controls. As with virtually all other aspects of the GMPs, the requirement to control manufacturing processes is hortatory only. “Specific control measures to be utilized are determined by the manufacturer.”⁵⁵ Such vaguely defined measures are meaningless.

J. Regulations concerning manufacturing should require strict quality control and quality acceptance criteria.

The proposed GMPs contain no meaningful requirements for quality control and quality acceptance. Such requirements are an essential element in any set of acceptable manufacturing practices.⁵⁶ The proposed GMPs would confine “procedures for nonconforming tobacco product” to any tobacco products that “do not meet specifications or are contaminated.”⁵⁷ However, as noted above, there are no meaningful standards for the setting of specifications and contamination is defined to exclude virtually every harmful constituent of the product. Moreover, the proposed GMPs would leave it to each individual manufacturer to establish such processes.

K. Manufacturing regulations should require the elimination of aflatoxin.

Aflatoxin is recognized as a carcinogen in tobacco products.⁵⁸ Unlike many other harmful constituents in tobacco products, which can be sharply reduced but not eliminated from such products, aflatoxin can be completely eliminated. Any acceptable manufacturing practice should require testing of each batch for aflatoxin and any other harmful constituent that can be eliminated from tobacco products.⁵⁹ No products containing any such constituent should be shipped.

⁵⁴ Attachment 2, *supra*, note 2, at 8, Section XXX.120.

⁵⁵ Attachment 2, *supra*, note 2, at 7.

⁵⁶ FDA Website. Drug Applications and Current Good Manufacturing Practice (CGMP) Regulations. Available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm090016.htm>. Accessed: May 8, 2013.

⁵⁷ Attachment 1, *supra*, note 53, at Subpart J XXX.130.

⁵⁸ FDA Website. Harmful and Potentially Harmful Constituents in Tobacco products and Tobacco Smoke: Established List. Available at: <http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm297786.htm>. Accessed: May 8, 2013.

⁵⁹ Standards for such constituents should be no less stringent than those that apply to food products.

L. Manufacturing regulations should require the maintenance of a master manufacturing record.

The requirement for development of a master manufacturing record is a potentially useful concept.⁶⁰ The Master Manufacturing Record is designed to include or reference the location of a number of pieces of potentially important information, including specifications, manufacturing methods, procedures and environmental requirements, quality control procedures, evaluation and quality control measures associated with reprocessing activities, label and packaging specifications, and methods and processes.⁶¹ Such a record is useful, however, only to the extent that its component parts are defined with sufficient specificity as to present an informative basis for evaluating the ability of the manufacturing facility to produce products that do, in fact, require tobacco products to present the lowest possible risk exposure to consumers. If the components are defined with appropriate specificity, the maintenance of such a master manufacturing record could be helpful in ensuring that the risk exposure presented by tobacco products is not inadvertently increased. It is clear that in the absence of regulatory requirements the industry will not develop effective procedures for providing such assurance.

M. Manufacturing regulations should establish consequences for a failure to comply.

The inadequacy of the proposed GMPs for tobacco products becomes more evident when they are compared to existing GMPs for drugs.⁶² The proposed GMPs for tobacco products leave so great a degree of discretion to manufacturers that they impose no real requirements. In addition, no consequence is provided for failure to comply. By contrast, the regulations applicable to drugs provide that “the failure to comply with any regulations set forth in this part . . . in the manufacture, processing, packing or holding of a drug shall render such drug to be adulterated under [the Food, Drug and Cosmetic] Act . . . and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.”⁶³ Any meaningful GMPs for tobacco products should contain similar provisions.

⁶⁰ Attachment 1, *supra*, note 53, at Section XXX.116, 11.

⁶¹ *Id.* at 11-12.

⁶² 21 CFR § 210-211

⁶³ 21 CFR § 210.1(b)