

HOW WOULD YOU REGULATE CIGARETTES IF YOU WERE DIRECTOR OF THE NEW FDA CENTER FOR TOBACCO PRODUCTS?

by

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We all know that FDA regulations are coming to the tobacco industry. What we do not know at this time (July 24) is how the FDA will implement through its regulations what Congress has mandated through legislation (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=111_cong_bills&docid=f:h1256enr.txt.pdf). Other than a few specifics [e.g., removal of characterizing flavors other than tobacco and menthol in cigarettes by September 22 – see Sec. 907 (a)(1)(A)], Congress has given the FDA much latitude on how it goes about regulating the tobacco industry. There are many unknowns; however, we have some ideas of what may happen. We also know that cigarettes, in particular, along with moist snuff, and novel forms of smokeless tobacco products are likely to get much more attention than the very traditional styles of pipe tobaccos and chewing tobaccos. Therefore, this discussion will focus on conventional cigarettes and will cover only manufacturing-related issues. Expected FDA regulations on PREPS and other reduced-risk products will be discussed in a separate document

Proponents of FDA regulation of cigarettes have focused on several manufacturing-related issues that the regulations should address: 1) menthol and other flavor-related additives that reportedly make cigarettes more attractive and easier to smoke; 2) tobacco and smoke nicotine levels and use of additives containing ammonia; 3) limits on smoke constituents, particularly tobacco specific nitrosamines (TSNAs); and 4) filter ventilation and other cigarette design parameters that allow smokers to inhale more smoke from each cigarette than was measured using the ISO standard or by the now defunct FTC method. However, other than the prohibition on characterizing flavors and the special provisions on menthol, many of the other provisions sought by the tobacco control community did not make it into the bill. They may come later as part of the regulations. This may appear as good news to the tobacco manufacturing community, but compliance with some of the bill's other provisions in the legislation may be more difficult and costly than it would be with a ban on all flavorings added to cigarette tobacco.

If we go to Sec. 906 (e) et seq., we see, “(e) GOOD MANUFACTURING PRACTICE REQUIREMENTS. — “(1) METHODS, FACILITIES, AND CONTROLS TO CONFORM.—

The FDA has several different versions of Good Manufacturing Practice, abbreviated GMP, and often cGMP, to refer to the current set of GMP rules for a given industry. There are no FDA cGMP for tobacco products. The FDA is either going to have to develop them and/or force-fit one or more of the existing sets of GMP rules onto tobacco manufacture. Some have suggested that cigarettes should be regulated as pharmaceuticals or as medical device (analogy to an asthma inhaler) with the tobacco

in them regulated as pharmaceutical product containing nicotine and additives. The FDA cGMP regulations for finished pharmaceutical products can be found at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211>. The cGMP rules for various medical devices can be found at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/MedicalDeviceQualitySystemsManual/UCM122806.pdf>. There are requirements for transmitting information to the FDA used to confirm that cGMP requirements are being followed. They can be found at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11>. A Google search of using ("cGMP" OR "21 CFR 11") AND consultants will give a listing of numerous consultants who are available to help clients understand the intricacies of these regulations.

Perhaps the thinking behind such an approach would be that the cost of compliance (even if delayed for four years for small tobacco manufacturers) would put many of the low-cost manufacturers out of business. Another reason for the pharmaceutical-style approach may be the mistaken belief that cigarettes will cause immediate injury or illness if not manufactured correctly (the dangers of cigarette smoking are from chronic use). Yes, there have been rare instances where foreign matter has inadvertently been mixed in with the tobacco in a cigarette to give a very noxious taste and odor to the smoke, but it is unlikely the testing and recordkeeping required by a pharmaceutical-style GMP would solve the foreign matter problem. Another reason for pharmaceutical-style GMP would be to make sure that nicotine or other additives regulated by the new law are not misused as some critics have suggested has happened in the past. There is no doubt that the chemical testing required to support the detailed analyses of every lot of tobacco used in cigarette manufacture and in every batch of finished cigarettes would require the hiring of many highly skilled chemists and technicians and require the purchase of much scientific equipment. It would also require standardized test methods for analytes that are not covered by today's methods such as those developed for Health Canada and as part of developing ISO standards for tobacco and cigarettes. Such a program could take years to complete; and regulations could be stymied until the proper test methods had been developed and validated.

Is there a better way and faster way that could be used to implement more sensible regulations? In many respects, the first part of a cigarette manufacturing plant, which is called the "primary," resembles a food plant that processes agricultural materials. Aged tobacco are blended, treated with additives such as aqueous mixtures of sugars, cocoa, and licorice, heated, cooled, remoistened, cut to the proper particle size for use in cigarettes, dried, flavored and stored until they are needed for cigarette manufacture. All the ingredients added to the tobacco are food grade and used in foods and beverages. Some of the equipment used to prepare the ingredients and process the tobaccos is similar to that used in the food industry. Many of the chemical compounds found in tobacco are also found in agricultural products used in foods. It would appear the FDA regulations for food cGMP would be a better fit. They are at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=110>. In-depth chemical analyses are generally not used to meet food cGMP requirements.

We do not expect a manufacturer of cookies to do sophisticated chemical analyses to verify that its workers have added the proper amount of a purchased flavor to the cookie dough. The correct amount of flavor is weighed out and added to the requisite amount of dough. The same approach is used for other ingredients such as the shortening and the leavening. For years, analytical chemists working with tobacco have used automated wet chemical and chromatographic analyses to characterize cigarette tobaccos before and after they go through the primary process. These are not detailed analyses of the many thousands of compounds in the tobacco, but the analyses focus on the major components nicotine and other alkaloids, sugars, and inorganic anions such as chloride, nitrate, and phosphate. Much of the process control is done with equipment that ensures that the correct amounts of additives are used for a given amount of tobacco.

Very important parts of food cGMP that should apply to tobacco are FDA's Hazard Analysis and Critical Control Point (HACCP) Systems. These can be found on-line at <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=120>. At several points in the processing of tobacco for use in cigarettes, the tobacco has a high enough water content to support microbial growth. Under some conditions, microbes can convert the endogenous nitrate in the tobacco to nitrite. Nitrite can react with nicotine and the secondary alkaloids in the tobacco to form tobacco specific nitrosamines (TSNAs). The same unfavorable chemistry can happen when reconstituted tobaccos are made and when stem is cut or shredded. All those operations are done with high levels of moisture. Tobaccos left on equipment will create problems. Points in the various processes where microbial growth is likely will need to be identified and steps taken to ensure minimal microbial growth. If the processes are in control, the final cut tobacco delivered to the cigarette makers should have consistent chemical properties, be free of foreign matter, and be at the correct moisture level.

Instead of force-fitting existing cGMP rules to conventional cigarette products, perhaps there should be a new category of product with its own GMP rules. Cigarettes are assembled from "parts" on highly precise automated equipment. The quality and conformance to specifications of each of those "parts" can be ascertained prior to their use in the cigarette manufacture. The parts of the common filter cigarette include 1) the tobacco (ready for use all processing completed), the filter (ready for use all processing completed), the cigarette paper, the sideseam adhesive (holds the paper around the tobacco to form the tobacco rod), the tipping paper (wraps around both the tobacco rod and the filter) and the tipping adhesive (holds the tipping paper to the cigarette rod and the filter). Depending on the brand-style there may be a monogram ink imprinted on the cigarette paper. If all the "parts" are within specifications, and the cigarette maker is properly maintained and setup correctly (tight control on tobacco weight and circumference), the chemical, physical properties of the cigarette will be constant. Likewise, the chemical, physical, and toxicological properties of the smoke will also be more consistent. The key parameters for a nonventilated filter cigarette are weight, circumference, and pressure drop. Automated instrumentation has been developed to measure these parameters on subsamples of each production run. These instruments

are based on ISO standards and are commercially available and have the potential for connectivity to information systems that meet 21 CFR Part 11.

In conclusion, by taking a sensible approach to GMP and using existing ISO standards and other common test methods, the path to effective regulation would be much smoother.