National Milk Producers Federation

2107 Wilson Blvd., Suite 600, Arlington, VA 22201 | (703) 243-6111 | www.nmpf.org

February 21, 2017

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

(Submitted electronically: www.regulations.gov)

Re: Docket No. FDA-2016-D-2343: Hazard Analysis and Risk-Based Preventive Controls for Human Food: Draft Guidance for Industry

Dear Sir or Madam:

The National Milk Producers Federation (NMPF) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) *Draft Guidance for Industry: Hazard Analysis and Risk-Based Preventive Controls for Human Food*. NMPF appreciates the effort that FDA has put into creating the document to assist the regulated community with compliance with the rule, and we would like to provide constructive comment on a number of areas.

FDA Definition of a Hazard Requiring a Preventive Control

FDA has defined a hazard requiring a preventive control as indicated below. It is a robust definition and clearly indicates that one should consider the severity of an illness or injury and the probability that the hazard will occur in the absence of a preventive control. While NMPF appreciates and agrees with the definition that has been submitted, as discussed in our comments that follow, NMPF feels some of the guidance document has strayed from this basic premise and should be re-evaluated.

> **Hazard requiring a preventive control:** A known or reasonably foreseeable hazard for which a person knowledgeable about the safe manufacturing, processing, packing, or holding of food would, based on the outcome of a hazard analysis (which includes the severity of the illness or injury if the hazard were to occur and the probability that the hazard will occur in the absence of preventive controls) establish one or more preventive controls to significantly minimize or prevent the hazard in a food and components to manage those controls (such as monitoring, corrections or corrective actions).

Drug Residues in Milk – Implications for Hazard Analysis

In FDA's guidance for conducting a hazard analysis, the recommendation is made that hazards potentially associated with a food or process (the "known or reasonably foreseeable hazards") be identified, referring to Chapter 3 and Appendix 1 to aid in identifying these hazards. These materials then refer to drug residues for consideration in dairy products. NMPF respectfully disagrees with FDA's conclusion that drug residues in dairy products represent a known or reasonably foreseeable hazard for several reasons.

First, the occurrence of drug residues in raw milk is very low. All Grade "A" raw milk, representing ~99+% of the US milk supply (USDA, 2015 data), is tested for Beta-lactams in accordance with Appendix N of the *Pasteurized Milk Ordinance*. Individual bulk milk samples from every producer are tested once monthly 4 times in every 6-month period. These test results, along with the results from other random testing by State Regulatory Agencies and individual milk processors, are compiled annually in the National Milk Drug Residue Database. The rate of residue-positive bulk milk pickup tankers has been steadily declining since 1996. The current fiscal year report[1] indicates a positive rate of 0.011% in bulk milk pickup tankers and no positive pasteurized retail products have been reported since 2010.

Second, there is no demonstrable evidence to suggest the presence of drug residues in milk or dairy products represents a human health risk. A thorough review of the scientific literature failed to identify any allergic reaction due to the presence of drug residues in milk[2]. There have been no case reports of allergic reactions to drug residues in milk since 1987, and those reported prior to 1987 are mostly circumstantial or anecdotal.

Two review articles (Dewdney, et al.[3] and Dewdney and Edwards[4]) recognize that, *theoretically*, drug residues in food could cause an immunological response; however, such a reaction is not probable and is not substantiated by scientific data. It is unlikely that drug residues in dairy foods contribute to an immune response given the very low levels that potentially occur, relative to the higher levels represented by a therapeutic dose during clinical treatment of an individual. Further, the oral route of administration has shown to be much less sensitizing than the parenteral route. In

[1] https://www.kandc-sbcc.com/nmdrd/fy-16.pdf, accessed February 16, 2017.
[2] World Health Organization. (2012), Evaluation of certain veterinary drug residues in food: seventy-fifth report of the Joint FAO/WHO Expert Committee on Food Additives. Technical report no. 969.
[3] Dewdney, JM, et al. (1991), "Risk assessment of antibiotic residues of β-lactams and macrolides in food products with regard to their immuno-allergic potential", Food Chem Toxic, **29**, 477-483.
[4] Dewney, JM and RG Edwards. (1984), "Penicillin hypersensitivity – is milk a significant hazard? A review", J R Soc Med, **77**, 866-877.

addition, immunochemical studies with penicillin indicate that the basic structure of the hapten-protein complexes, formed *in vivo* after penicillin administration, is not immunogenic because of the low dose, low epitope density and binding to autologous carrier proteins. No documented evidence is available to suggest that an individual has become sensitized by residues of penicillins or macrolides[5,6]. In terms of the *theoretical* potential that drug residues could result in allergic reactions in individuals with extreme sensitivity, the low dose and low degree of dairy product substitution are arguments in favor of low allergenicity of residues – which is further substantiated by a lack of well-documented case reports.

In the dairy industry, antimicrobials are used at specific points in time for the prevention and treatment of disease; they are not widely used as feed supplements for enhanced growth (i.e., sub-therapeutically). Of the antimicrobials administered by dairy producers to lactating dairy cows, beta-lactams are estimated to be the most common (more than 70% of the antibiotics used to treat clinical mastitis in lactating dairy cows are beta-lactams[7]). Given the use of beta-lactam antibiotics in dairy production and the high degree to which beta-lactam sensitivity is diagnosed (~10% of the population reporting such an allergy[8]), the lack of data linking drug residues in milk to a human health risk is worth noting. Scientific reviews have not substantiated a health risk due to drug residues in milk, and have concluded that they are not a clinical hazard[9]. As stated by Dewdney et al.[10], "the residue issue for beta-lactams is more a perceived than a real problem". It would be disingenuous, and scientifically irresponsible, for FDA to continue such a misperception through this current guidance document.

NMPF must note that we are not advocating for disregard of the current beta-lactam testing program; however, it is imperative to clarify that testing for drug residues is not because of a food safety concern. Decades ago, the initial concerns about drug residues in milk were from dairy processors challenged by starter culture inhibition.

---

[5] World Health Organization. (2012), Evaluation of certain veterinary drug residues in food : seventy-fifth report of the Joint FAO/WHO Expert Committee on Food Additives. Technical report no. 969.

[6] Dewdney, JM, et al. (1991), "Risk assessment of antibiotic residues of β-lactams and macrolides in food products with regard to their immuno-allergic potential", Food Chem Toxic, **29**, 477-483.

[7] USDA-APHIS-VS (2016), "Dairy 2014, Milk quality, milking procedures, and mastitis on U.S. dairies", National Animal Health Monitoring System, accessed February 16, 2017 https://www.aphis.usda.gov/animal_health/nahms/dairy/downloads/dairy14/Dairy14_dr_Mastitis.pdf.

[8] Solensky, R. (2003), "Hypersensitivity reactions to beta-lactam antibiotics", Clin Rev Allergy Immunol, **24**, 201-219.

[9] Dewney, JM and RG Edwards. (1984), "Penicillin hypersensitivity – is milk a significant hazard? A review", J R Soc Med, **77**, 866-877.

[10] Dewdney, JM, et al. (1991), "Risk assessment of antibiotic residues of β-lactams and macrolides in food products with regard to their immuno-allergic potential", Food Chem Toxic, **29**, 477-483.

Then the discussion turned to needing to protect hypersensitive individuals from potential allergic reactions, which has never been clearly demonstrated. The current guidance document refers to short-term effects of drug residues (allergic reaction) and cites an article by Dayan[11] – but, in fact, this review article, for reasons stated above, concludes that drug residues would not be considered a risk to human health. The guidance also refers to potential long-term effects (development of drug-resistant bacteria), but this is not addressed by the article by Dayan and the relationship between antibiotic residues in milk and the development or transfer of resistant pathogens appears to still be hypothetical. The direct transfer of resistant organisms to humans through consumption of milk is unlikely because most dairy products are made from pasteurized milk. If FDA is aware of a health risk represented by drug residues in milk, we ask that they share the data and the peer-reviewed scientific articles to support such a claim (the Dayan article that was cited does not).

In sum, testing of raw milk for drug residues is not done as a food safety concern, rather, at the levels for which milk is currently being tested for residues, the presence indicates adulteration under the federal Food Drug and Cosmetic Act. For that reason, NMPF feels the guidance document should not reference drug residues in milk and dairy products as a chemical hazard. Testing for drug residues as is done to meet the requirements of the *Pasteurized Milk Ordinance* as a pre-requisite program is extremely effective at limiting the occurrence of drug residues in the milk supply. The focus should remain on compliance with drug residue testing protocols, allowing facilities to spend limited resources on true, rather than perceived, food safety hazards.

Lactose as a Chemical Hazard

The current guidance refers to food additives, color additives, and GRAS substances, including substances associated with food intolerance or food disorder (page 67). When giving examples of such substances that have been linked to food intolerances, lactose is included. The specific text is below:

> **Lactose:** Some people are intolerant to lactose, a sugar that is a component of milk, because they lack the enzyme to digest lactose. The symptoms include abdominal pain, diarrhea, vomiting, gas, cramps or bloating. People who have a lactose intolerance avoid milk or milk products and rely on the allergen labeling for milk to identify the types of products that may cause them problems.

NMPF must insist on FDA's removing of the third sentence of the paragraph above, specifically that people who are lactose intolerant "rely on the allergen labeling for

[11] Dayan, AD. (1993), "Allergy to antimicrobial residues in food: Assessment of the risk to man", Vet Microbiol, **35**, 213-226.

milk to identify the types of products that may cause them problems". People who are truly allergic to milk protein know that the presence of "lactose" in an ingredient statement does not mean they would have an allergic reaction. Likewise, a food might be properly labeled with an allergen statement noting that the food contains milk protein, and a person who is lactose intolerant (LI) may have no symptoms of LI after consuming that food.

Lactose intolerance is the inability to digest milk sugar. Allergen labeling is required when milk protein is present. The Food Allergen Labeling and Consumer Protection Act (FALCPA) of 2004 refers to the "big eight" foods and ingredients that contain protein derived from those eight foods. FALCPA requires either (1) the name of the food source in parenthesis following the common or usual name of the major food allergen in the list of ingredients in instances when the name of the food source of the major allergen does not appear elsewhere in the ingredient statement (e.g., "casein (milk)"), or (2) the name of the food source from which the major food allergen is derived either immediately after or adjacent to the list of ingredients (e.g., "contains milk"). However, lactose is not a protein. While a product that contains the milk-derived protein casein would have to use on the label the term "milk" in addition to the term "casein" – so that those with milk allergies would clearly understand the presence of an allergen they need to avoid – no such labeling requirement applies when lactose is used as an ingredient as it does not contain an allergenic protein. Therefore, NMPF respectfully requests the text accompanying "lactose" be re-written so as not to confuse milk protein allergies and lactose intolerance.

Hazard Analysis for No/Low Probability Events

Logic would dictate that when there is a zero or near-zero probability that an illness or injury will occur, that potential hazard should not be considered or analyzed further. FDA's guidance, however, seems to raise many theoretical potential hazards for the regulated community to consider, radiological hazards as one example. The guidance states:

> **Radiological hazards**
>
> Radiological hazards rarely occur in the food supply; however, when they do occur, these hazards can present a significant risk when exposures occur over a period of time (WHO, 2011). Consuming food contaminated with radionuclides will increase the amount of radioactivity a person is exposed to, which could have adverse health effects. The health effect depends on the radionuclide and the amount of radiation to which a person is exposed. For instance, exposure to certain levels of radioactive iodine is associated with increased risk of thyroid cancer (WHO, 2011).

Radiological hazards can become incorporated into food through the use of water that contains the radionuclides during food production or manufacture. There are areas in the United States where high concentrations of some radionuclides, such as radium-226, radium-228, and uranium, can be detected in well water (Ayotte et al., 2007; Focazio et al., 2001). You should be aware of the condition of the water used for production and manufacture in your facilities. For example, if your facility uses well water and there are elevated levels of radionuclides in the well water, you should not use the water. The CGMPs require that water that contacts food, food-contact surfaces, or food-packaging materials be safe and of adequate sanitary quality (see 21 CFR 117.37(a)).

Radiological hazards also may result from accidental contamination, e.g., contamination arising from accidental release from a nuclear facility or from damage to a nuclear facility from a natural disaster. In 2011, following damage to a nuclear power plant during an earthquake and tsunami in Japan, radioactivity was subsequently detected in foods, particularly milk, vegetables, and seafood produced in areas neighboring the plant (WHO, 2011). You should be vigilant regarding accidental releases of radiological hazards and their potential to contaminate your food product, either directly due to contamination of natural resources near your facility or as a result of raw materials and other ingredients that you obtain from a region that has experienced an accidental release of radiation.

Radiological hazards have virtually zero probability of materializing without being noticed in advance of food processing and food distribution. Nuclear power plants routinely test for radiological releases in and around their facilities, including vegetation, water and milk. The Environmental Protection Agency has a well-established program, RadNet, which routinely tests for radiation. In fact, it was the RadNet testing program that provided robust data when the nuclear reactors in Fukushima failed. Ultimately a small number of samples of milk in the U.S. tested positive which FDA mentioned in a March 2014 press release, acknowledging it was not a public health threat:

The U.S. Environmental Protection Agency (EPA) has reported low levels of radionuclides in milk in the U.S. Is this a cause for concern?

At this time, there is no radiation safety risk related to milk produced in the U.S. EPA monitors milk for radiation under its RADNET program, and has reported extremely low levels of I-131 and Cesium in some milk samples. These results are expected and are far below FDA's Derived Intervention Levels. Even for a

> person who drinks a lot of milk, it would be virtually impossible to consume enough milk to approach the level of concern.
>
> As federal and state agencies test milk samples, low levels of I-131 may be found in different samples, and the levels may vary slightly. However, these low levels are not expected to cause adverse health effects, even for the developing fetus, babies, or children. At this time, there is no public health threat in the U.S. related to radiation exposure. FDA, together with other agencies, is carefully monitoring any possibility for distribution of radiation to the United States. At this time, theoretical models do not indicate that significant amounts of radiation will reach the U.S. Please see **www.epa.gov** for more information about monitoring efforts.

Radiation does not sneak up on us; and where it could be a problem, adequate detection systems are in place. If nuclear reactors were to fail in this country or near our borders, then the food industry should revisit their hazard analyses. However, encouraging the regulated community to routinely consider radiological hazards is not an efficient or judicious use of resources. Further, there is concern that well-intentioned inspectors will routinely look at facilities' hazard analyses and debit the facility owner for not addressing radiological hazards.

FDA's guidance also raises the issue of micro-contaminants in food in multiple locations in the guidance, specifically dioxins and dioxin-like PCBs.

> Environmental contaminants may be of concern in certain foods as a result of their presence in the environment. When your hazard analysis identifies an environmental contaminant that requires a preventive control, the type of control would depend on how the environmental contaminant could get into your food product. In some cases, high levels of environmental contaminants (e.g., dioxin) may result from accidental contamination of animal feed (WHO, 2014). In 2008, pork meat and pork products were recalled in Ireland when up to 200 times the safe limit of dioxins were detected in samples of pork, although risk assessments indicated no public health concern. The contamination was traced back to contaminated feed. In 1999, high levels of dioxins were found in poultry and eggs from Belgium and in several other countries. The cause was traced to animal feed contaminated with illegally disposed PCB-based waste industrial oil. Because dioxins tend to accumulate in the fat of food-producing animals, consumption of animal-derived foods (e.g., meat, poultry, eggs, fish, and dairy products) is considered to be the major route of human exposure, and FDA has developed a strategy for monitoring, method development, and reducing human exposure (FDA, 2002).

> FDA has set action levels and tolerances for some contaminants (FDA, 2015f). They represent limits at or above which FDA will take legal action to remove products from the market. Where no established action level or tolerance exists, FDA may take legal action against the product at the minimal detectable level of the contaminant. Action levels and tolerances are established based on the unavoidability of the poisonous or deleterious substances and do not represent permissible levels of contamination where it is avoidable. For example, FDA has established an action level of 3 ppm polychlorinated biphenyl (PCB) residues in red meat on a fat basis (FDA, 1987). FDA also has issued for public comment a draft guidance for industry that would, when finalized, establish an action level of 100 ppb for inorganic arsenic in infant rice cereal (FDA 2016). FDA has established tolerances for polychlorinated biphenyls (PCB's) in foods such as milk and other dairy products, poultry, eggs, and infant and junior foods (see 21 CFR 109.30).

We suggest that FDA revisit the Interagency talking points on Dioxin and Dioxin-like like substances which was circulated a number of years ago (but is now unfortunately absent from FDA website). PCB's are a dioxin-like chemical. In that document, you will see the following:

> The most well-established health effect in people exposed to unusually large amounts of dioxin is chloracne, a skin disease of varying severity with acne-like lesions that occur mainly on the face and upper body. Such levels have typically been the result of accidents, intentional poisonings or significant contamination events. Other effects of exposure to large amounts of dioxin include skin rashes, skin discoloration, excessive body hair, and possibly mild liver damage.
>
> **Is the food supply safe?**
> Yes, the U.S. food supply is among the safest and most nutritious in the world. While the federal food and environmental agencies are concerned about dioxin, the draft report does not change the government's view of the overall safety of the food supply in this country. Maintaining the safety of the food supply is a top U.S. government priority.
>
> **Should I stop eating particular foods?**
> No, we do not recommend avoiding particular foods because of dioxins. The draft dioxin report from EPA indicates that following the science-based advice in the Dietary Guidelines for Americans will also likely help individuals lower their risk of exposure to dioxins. These guidelines include the recommendations to

choose meat and dairy products that are lean, low fat, or fat free and to increase consumption of fruits, vegetable, and grain products.
Meat, milk, and fish are important sources of nutrients for the American public and an appropriate part of a balanced diet. Milk is a major source of calcium, vitamins A and D, and riboflavin; meat is an important source of iron, zinc and several B-vitamins; fish provides beneficial fatty acids as well as certain vitamins and minerals. Each of these foods provides high quality protein in the diet. Lean meat includes meats that are naturally lower in fat, and meat where visible fat has been trimmed. For fish and poultry, you can reduce fat by removing the skin. Reducing the amount of butter or lard used in the preparation of foods and cooking methods that reduce fat (such as oven broiling) will also lower the risk of exposure to dioxin.

These strategies help lower the intake of saturated fats as well as reduce the risk of exposure to dioxin. Similarly, the 2003 NAS report titled "Dioxins and Dioxin-like Compounds in the Food Supply: Strategies to Decrease Exposure" identified promoting changes in dietary consumption patterns of the general population that more closely conform to recommendations to reduce consumption of animal fats, such as the recommendations of the Dietary Guidelines for Americans, as options to be considered to reduce dioxin exposure through food-consumption pathways. For information on the Federal Dietary Guidelines see www.health.gov/dietaryguidelines/.

There is dioxin in the environment, and there always will be given that the single largest source is forest fires. Other than forest fires and backyard barrel burning, most sources of dioxin and PCB's have been eliminated. FDA is well aware that dioxin levels in the food supply are negligible and are going down, and therefore, they do not constitute a public health hazard for which a preventive control is needed.

Spreading Resources Too Thinly To Account for Unlikely Scenarios
Further, no matter how thoroughly one plans, the unlikely will occur. When it does, we should jump into action, accept that and be responsive. The food industry did this when Fukushima occurred, and we continue do this periodically when aflatoxin situations arise. Temporal adverse events warrant consideration when conditions so dictate, but they should not be part of our everyday life and they should not distract our attention from those things that we know we need to focus on.

For example, it is clear that North Korea would like to develop a long range missile that can deliver a nuclear warhead to U.S. soil. The probability of that happening anytime soon is very low, though the severity should it occur is high. However, that

does not warrant the inclusion of a North Korean nuclear strike in every food processor's hazard analysis.

It is not reasonable to consider every imaginable hazard, no matter how low the probability of occurrence is. FDA's definition is clear, we must consider both the probability and severity of illness and injury. Where the probability is low or approaches zero and the likelihood that any injury or illness would be minimal, we should not include those scenarios in a hazard analysis. When the probability is low but the severity high, as in the aforementioned North Korean nuclear scenario, common sense and judgement need to be applied.

When FDA trains its inspection staff, FDA should make it very clear there are few things in life that are black and white, and who is reasonable and who is not is at best murky. A responsible facility using their reasonable judgement should be given some deference during the course on an inspection or evaluation. FDA's guidance should convey and emphasize reasonable minds may reach differing conclusions and embrace that.

NMPF Concurs with Guidance on Melamine in Raw Milk

NMPF concurs with FDA's guidance on the issue of melamine in milk. The unfortunate incident to which the guidance refers is one example of economically motivated adulteration that occurred in China. Thankfully that sort of criminal behavior is not occurring in the U.S. and we do not envision it ever happening in this country. NMPF agrees that one should not consider the potential for melamine being present in domestic milk.

> In determining whether a hazard that may be intentionally introduced for purposes of economic gain is a hazard requiring a preventive control, we recommend that your hazard analysis consider both the country of origin of an ingredient that may contain the hazard and any specific supplier associated with an ingredient containing that hazard. For example, one example listed in Table 3-8 is a widespread incident of economically motivated adulteration in which some milk firms in one country added melamine, a nitrogen-rich industrial by-product, to diluted dairy products to increase the apparent protein content (FDA, 2008). This adulteration resulted in significant public health consequences, with more than 290,000 ill infants and 6 deaths in that country. In light of this incident, we recommend that you include in your hazard analysis the potential for melamine to be an economically motivated adulterant in your food products when using milk products from a country where melamine adulteration has occurred and, based on the outcome of that hazard analysis, determine whether melamine is a hazard that must be addressed in your food

safety plan. At present, we do not expect you to consider the potential for melamine to be a significant hazard when using domestic milk products, or milk products from other countries when there is no history of melamine adulteration associated with those countries.

NMPF Concurs that Pathogens in Raw Milk Products Are Hazards

NMPF concurs with FDA position that *Brucella* and other pathogenic bacteria should be considered in a facility's hazard analysis when producing raw milk products. Most milk and milk products are pasteurized, which eliminates the potential problem.

> **Brucella sp** is the bacterium responsible for brucellosis. An estimated 840 foodborne cases of brucellosis occur annually in the United States (Scallan et al., 2011) When sheep, goats, cows, or camels are infected with the pathogen, their milk becomes contaminated with the bacteria. The most common way for humans to be infected is by eating or drinking unpasteurized/raw dairy products from infected animals. *Brucella* can also enter the body through skin wounds or mucous membranes following contact with infected animals. Symptoms include: fever; sweats; malaise; anorexia; headache; pain in muscles, joints and/or back; and fatigue. Some signs and symptoms may persist for prolonged periods of time or may never go away.

* * * * * * * *

NMPF appreciates the effort that FDA has put into the guidance document and we believe it is a valuable tool to assisting the regulated community achieve compliance. We are concerned, as indicated above, that FDA has raised a few too many theoretical hazards that are unlikely to occur or have little or no public health threat. Encouraging the regulated community to consider excessive numbers of hazards will not enhance the quality of a hazard analysis or a food safety plan, rather, it will detract from it. We respectfully request that FDA to remove unlikely hazards from future guidance as it only encourages the regulated community and inspectors to spend time in areas that do not contribute to our overall food safety objectives.

Respectfully Submitted by,

Clay Detlefsen
Senior Vice President, Environmental
and Regulatory Affairs & Staff Counsel

Beth Briczinski, Ph.D.
Vice President, Dairy Foods & Nutrition

The National Milk Producers Federation, based in Arlington, VA, develops and carries out policies that advance the well-being of dairy producers and the cooperatives they own. The members of NMPF's cooperatives produce the majority of the U.S. milk supply, making NMPF the voice of more than 32,000 dairy producers on Capitol Hill and with government agencies. Visit www.nmpf.org for more information.