Safety Assessment of BPA in Medical Products

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The Food and Drug Administration (FDA), at the request of the Commissioner, has initiated an assessment of the potential risks posed by exposure to Bisphenol-A in medical products (medical devices, drugs and biologics). This document: 1) outlines the approach the FDA plans to use to assess the risk posed by exposure to BPA from medical products and 2) seeks input on a number of cross-cutting science and science policy issues. Review of this methodology document provides the FDA's Science Board with the opportunity to influence the priorities and direction of the Agency's plan.

Public Health Implications

The Agency proposes this plan in the context of its mission to protect and preserve the public health. The three components of this plan consist of the preclinical, clinical and epidemiologic investigations of BPA. And as is the case for any chemical used for human therapeutic purposes, the preclinical investigation is the most appropriate to identify the pharmacokinetics, pharmacodynamics and toxicology of the compound, while the clinical studies evaluate these parameters in humans. Epidemiologic studies focus on associations between the compound and rare adverse events in particular patient populations.

Goals of this Report

1.0 Introduction

1.1 *Report Objectives*

The Agency requests input from Science Board on the validity of the plan described herein as well as input on any/all additional scientific issues relevant for assessing the risk posed by exposure of individuals to BPA from the wide range of FDA-regulated products.

1.2 *Scientific Objectives*

FDA's Center for Devices and Radiological Health (CDRH) will integrate existing preclinical, clinical and epidemiologic data from the scientific literature to assess the safety of BPA in medical products and to determine the future course of scientific research.

In parallel, CDRH will conduct select studies as are technically feasible in areas deemed potential "worst case" scenarios, providing additional insight for the future course of scientific research.

Readers will note that the document primarily focuses on medical devices, deemed to be the most relevant for this assessment of BPA, though input from FDA's Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) has and will be sought.

2.0 Methods

Critical to the assessment of BPA's potential effects is an understanding of acceptable exposure. The

level of acceptable exposure is based on the Tolerable Intake (TI) value derived for the compound from data in the scientific literature and risk-benefit considerations, such as those discussed above. The approach that the FDA intends to use to derive the TI value for BPA is outlined below.

2.1 General approach

Determining the acceptable level of clinical risk posed by exposure of patients to BPA from medical products is only possible within the context of the clinical benefit of the use of the product in question. Thus the preclinical component of the program will focus on safety by comparing the doses of BPA received by patients undergoing various procedures to Tolerable Intake (TI) values for BPA. A TI value is the dose of a compound that is not expected to produce adverse effects in humans following exposure for a defined period. The process used by CDRH and by regulatory agencies in other countries responsible for medical device safety to derive the TI values is outlined in ISO 10993-17:2002 standard, *Method for the Establishment of Allowable Limits for Leachable Substances.* The ISO standard was accepted as a US standard in 2002. The ISO 10993-17 process is described more fully in Section 2.3, but briefly consists of three steps:

Step 1: Identification of data from critical studies to serve as the basis for the selection of no-observed- adverse-effect-level (NOAEL) and lowest observed adverse effect-level (LOAEL) or dose-response data that can serve as the basis for a benchmark dose (BMD) analysis.

Step 2: Derivation of Uncertainty Factors (UFs) to account for: 1) variability in response in the human population, 2) differences in the potency of BPA between experimental animals and humans, and 3) various other limitations in the database.

Step 3: The NOAEL/LOAEL or BMD values selected from the critical studies were then divided by the product of the UFs (known as the Modifying Factor) to derive the TI.

To characterize the potential risk posed by exposure to BPA, the dose of BPA received by patients undergoing various procedures, estimated in the exposure assessment step, will be compared to the parenteral TI value derived for BPA in the toxicity assessment step. This process is described more fully below in Section 2.3. Comparison of the estimated dose and the TI will allow us to draw conclusions about the potential risk posed by patient exposure to BPA in various clinical scenarios. This approach is conceptually similar to that used by CDER (FDA, 2005) in determining maximum safe starting doses in initial clinical trials and is identical to the approach used by CDRH (FDA, 2001) to assess the risk posed by patients exposed to DEHP released from medical devices. Further, CDRH uses this approach on a routine basis on a preclinical and post-market basis to assess the risk posed by exposure of patients to compounds released from medical device materials.

The FDA is referring to this process as a "safety assessment" rather than a "risk assessment", since the Agency will not be providing a quantitative estimate of risk posed by exposure of patients to a given dose of BPA (e.g., a risk of 1 in 10,000 of an adverse effect occurring following exposure to a specific dose of BPA). As discussed in Section 2.5, Risk Characterization, the estimated dose will be compared to the TI. If the dose exceeds the TI (dose/TI ratio > 1), then both scientific and risk management factors go into determining the acceptability of the dose/TI ratio, including the severity of the endpoint used to derive the TI, the value selected for the modifying factor, the size of the exposed population, the availability of alternatives to the compound, the potential that the properties or biocompatibility of the device may be altered by the use of alternatives, and the benefits conferred by the clinical use of the device.

It is important to recognize that the TI is derived for the compound, in this case, BPA, but the bioavailable dose (exposure) is determined on a device-by-device basis or for a given procedure. Because the bioavailable dose and the risk-benefit relationship may be different for various BPA-containing devices, the acceptability of the dose/TI ratio for a compound will be evaluated on a device-by-device basis. As detailed in the clinical section, this plan includes direct assessment in two clinical

scenarios that appear to be likely to represent high exposure, cardiopulmonary bypass and hemodialysis. Integration of the preclinical and clinical will permit more robust conclusions and inferences regarding the acceptability of BPA exposure in medical products with direct blood contact.

2.2 Exposure Assessment

2.2.1 Medical Devices

The FDA will be employing a three-pronged approach to obtain data on the dose of BPA received by patients. First, the literature will be searched to identify relevant studies. Second, chemists in the CDRH Office of Science and Engineering Laboratories (OSEL), Division of Chemistry and Materials Science (DCMS), will identify devices that can theoretically release BPA based on their constituent materials. And third, experts in each relevant product review division in CDRH and CBER will be asked to identify devices with polycarbonate or polysulfone components and devices that contain resins such as bisphenol A diglycidylether methacrylate (Bis-GMA) that can release BPA upon degradation. Initial efforts have begun to assemble this information and prepare the exposure assessment.

The preliminary results of our exposure assessment indicate that limited data are available to estimate the dose of BPA patients receive following the application of dental sealants, but essentially no data exist to quantify the dose of BPA patients receive undergoing medical procedures like cardiopulmonary bypass and hemodialysis. Our approach to obtain these data includes the following steps:

- ☐ FDA issued an FR notice (FDA, 2008) on October 18, 2008 requesting data from manufacturers and other stakeholders on the presence of BPA in medical devices and, if known, on the amount of BPA released following clinical use of the device.

- ☐ CDRH is initiating studies to quantify the dose of BPA released from a closed-loop hemodialysis circuit (modeled circuit) and the dose of BPA received by pediatric patients following cardiopulmonary bypass (clinical study). Studies are also planned to quantify BPA release from a variety of polymers under clinically relevant extraction conditions and to examine the impact on material properties when alternatives to BPA are used in the polymer.

- ☐ FDA has contacted Health Canada and requested any information they might have on how BPA is used in the manufacturing of medical devices.

As a practical matter, the current lack of accurate data on the dose of BPA patients receive limits the ability of CDRH to assess the potential risk of exposure to this compound from device-related sources.

2.2.2 Drugs

The greatest risk of BPA leaching into a drug formulation is most likely to occur with liquid and suspension formulations that are packaged in (i.e., direct contact with) polycarbonate container-closures or metal canisters with epoxy lining. Therefore, CDER will focusing on assessing the potential for exposure to BPA from use of these products.

Our electronic database of product information has been searched for references to the words: *bisphenol A*, polycarbonate, and epoxy lining/coating. The FDA has also conducted a survey of our product quality review staff to gather information from their reviews of drug applications regarding:

- Amount of BPA either as a component of or as a fabrication process aid for the container closure system (CCS),
- Amount of BPA observed as an extractable from the CCS and acceptance criterion, and
- Amount of BPA observed as a leachable from the CCS into the drug product, and acceptance criterion.

Out of the thousands of approved products in our database, to date CDER has identified eight drug products that could potentially contain *bisphenol A* either as an extractable in the container closure or as a leachable in the formulation. One of these is orally administered, three are injectables, and four are inhaled products. None of the applicants reported detectable levels of BPA in their products. The limits of detection were in parts per million (ppm) range or lower and the dosages are such that potential exposure to BPA would be in the microgram range or lower.

2.3 Toxicity Assessment

The goal of the toxicity assessment is to identify an appropriate toxicological "point of departure" for the dose-response relationship to calculate a Tolerable Intake (TI) value for BPA. This point of departure will either be a No-Observed-Adverse-Effect-Level (NOAEL) identified from a relevant study or group of studies, or a value based on Benchmark Dose (BMD) modeling, if appropriate dose-response data are available.

As mentioned above, this approach involves the following steps. Following a comprehensive review of the literature, data from critical studies will be identified to serve as the basis for the selection of NOAEL or BMD (Step 1). The scientific merits and limitations of studies that reported the highest NOAELs and lowest LOAELs following parenteral administration of BPA to experimental animals will be reviewed in the safety assessment to illustrate how the critical values were selected. Once the most appropriate NOAEL/LOAEL or BMD values are selected, Uncertainty Factors (UFs) will be derived to account for: 1) variability in response in the human population, 2) assumed differences in the potency of BPA between experimental animals and humans, and 3) various other limitations in the database (Step 2). The NOAEL/LOAEL or BMD values selected from the critical studies will then be divided by the product of the UFs (known as the Modifying Factor) to derive the TI (Step 3):

$$\text{TI (mg/kg/day)} = \frac{\text{NOAEL/LOAEL or BMD (mg/kg/day)}}{\text{Modifying Factor}}$$

Since the potency of BPA differs following oral and parenteral administration, due to extensive first-pass metabolism, it is necessary to derive separate TIs for oral and parenteral exposure to the compound. To promote regulatory consistency across Centers, CDRH plans to rely on the results of the safety assessment performed by CFSAN as the basis for the oral TI value for BPA.

A parenteral TI will be derived for BPA in the safety assessment that will presumably be relevant and adequately protective for all parenteral routes (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular), except intracerebroventricular (ICV).

2.3.1 Inclusion/exclusion criteria for selecting studies

2.3.1.1 Inclusion criteria

Any paper published in a peer reviewed journal describing a study in which BPA was administered to mammalian experimental animals (or humans) by a parenteral route of exposure (except ICV) will be

initially considered. The Toxicity Working Group recognizes that most toxicity studies conducted by researchers in academia are not conducted using GLP; nevertheless, these studies may be useful for the risk assessment process. As a result, non-GLP studies will be included in the evaluation. Further, there will be no *a priori* requirement that the study report the purity of the BPA, whether a low phytoestrogen diet was used, or which caging/bedding materials were used, but such information is useful. Also, the study does not need to report plasma BPA levels associated with toxic effects to be considered for further evaluation. Although multi-dose studies are preferred, studies that used only one or a few doses will not be automatically excluded for consideration.

Although the clinically relevant parenteral route of exposure to BPA from medical devices is likely to be intravenous, data from studies that employed any parenteral dosing route other than ICV are assumed to be relevant for derivation of the parenteral TI.

2.3.1.2 Exclusion criteria

Exclusion criteria for studies included oral exposure studies, *in vitro* or pharmacokinetic studies, studies with a small sample size or ones in which a statistically significant change in a parameter was not reported, studies involving non-mammalian species, and studies in which the effects were only seen at relatively high doses (≥ 10 mg/kg/day).

2.3.1.3 What represents an adverse effect for the purpose of TI generation?

Derivation of a non-cancer TI value for BPA or any compound released from a medical device material requires identification of NOAEL/LOAEL or appropriate dose-response data for the derivation of a BMD. A key element in the selection of the most appropriate dose level for risk assessment purposes is the determination of what types of toxicological endpoints represent an adverse effect.

There are certain effects that are indisputably adverse (e.g., death); however, there are many physiological changes that occur in animals and humans exposed to a chemical compound that may not be adverse, *per se*, but rather are adaptive changes. For example, changes in enzyme levels or gene expression in tissues are not typically considered to be adverse for risk assessment purposes.

During our preliminary efforts to identify data that could serve as the basis for the TI, the CDRH BPA Toxicity Working Group selected studies in which the endpoints involved histopathological or morphological changes to organs or tissues, or statistically significant changes in tissue weight or body weight. Biochemical or hormonal changes alone were not considered to be sufficient to serve as the basis for TI generation; however, these effects can serve as useful and important supporting data. Changes in sperm count or quality, changes in fertility indices, and teratogenic effects in fetuses or newborns are considered to be adverse for the purposes of this risk assessment. The toxicological significance of some hormonally mediated effects, like reduced anogenital distance in newborn animals, is a topic of active discussion in the risk assessment community. These effects will be considered on a case-by-case basis, depending on the study. Since this is a cross-cutting issue, the FDA recommends that the toxicological significance of hormonally mediated effects be evaluated on an Inter-Center basis.

The CDRH BPA Toxicity Working Group is currently assessing the toxicological significance of the neurological and neurobehavioral effects seen in BPA-treated animals; however, since these effects can be seen following oral and parenteral administration of BPA to experimental animals, it would be useful to evaluate the significance of these effects on an Inter-Center basis.

2.3.1.4 "Low dose" effects

The relevance of low-dose effects seen in bisphenol A-exposed experimental animals for human health risk assessment is a subject of considerable debate and controversy in the scientific community. This is

especially important for assessing the safety of BPA released from medical devices, since some studies (e.g., Honma et al., 2002) determined to be "adequate" by the CERHR expert panel report adverse reproductive and developmental effects after low does exposure of experimental animals to BPA by parenteral routes. Because of the implications of this issue for multiple FDA-regulated products, the FDA recommends that this issue be addressed on an Inter-Center basis to promote regulatory consistency across Centers.

2.3.1.5. Human studies

No studies have been conducted to investigate the potential adverse effects of BPA in patients undergoing medical procedures; however, several studies have been published recently that suggest that BPA exposure is associated with the development of adverse effects in humans. Notably, Lang et al. (2008) recently reported that elevated BPA concentrations were associated with an increased risk of diabetes and elevated liver enzymes in individuals participating in the 2003-2004 National Health and Nutrition Examination Survey (NHANES) study. It is important to keep in mind, however, that the exposure scenarios in these studies are very different from those associated with medical device use. With the case of dental sealants, exposure only lasts for 1 hour at most, compared to repeated daily exposure for food-related sources. Also, there are considerable difficulties in identifying long-term reproductive/developmental changes in adults that are attributed to exposure of the individuals to compounds released from medical devices when they were infants or children, as illustrated by Rais-Bahrami et al. (2004). These issues raise questions about the relevance of these studies for TI derivation. As a result, the FDA recommends Inter-Center input on how human studies can be used to evaluate the safety of BPA in medical devices, and, more broadly, all FDA-regulated products.

In conjunction with CFSAN, CDRH epidemiologists are working with NIH and CDC to determine whether completed and/or ongoing clinical studies may provide opportunities to gain insight regarding any potential relationships between BPA exposure and clinical risk. This work is in very preliminary stages and is focused currently on review of the studies funded by NIH that have urine samples collected and stored adequately for measurement of BPA levels, within which relevant clinical event data are/were collected. A major goal is to provide further epidemiologic insights, particularly with respect to risk of BPA exposure to adults.

2.3.2 Selection of relevant toxicity studies to assess potential noncancer risk

The CDRH BPA Toxicity Working Group is currently evaluating the scientific merit of the published studies that could serve as the basis for the parenteral TI for BPA. This working group is composed of toxicologists from OSEL and ODE with expertise in reproductive toxicology and neurotoxicology.

In addition to conducting an independent review of the studies in the literature, the CDRH BPA Toxicity Working Group will carefully consider the opinions of the CERHR expert panel regarding the acceptability of these studies for regulatory decision making.

In our preliminary review of the data, the BPA Toxicity Working Group has identified a number of studies that could serve as the basis for a parenteral TI value for BPA. However, rather than basing the TI on the results of one particular study, CDRH is proposing to use a weight of evidence approach to select a point of departure for TI derivation. Since the identification of a NOAEL or LOAEL is dependent on the doses investigators conducting each study select, evaluation of a range of values from well-conducted studies allows a weight-of-evidence approach to select the aggregate NOAEL or point of departure that best represents the dose of BPA that is not likely to produce adverse effects in experimental animals. CDRH believes this approach permits a robust assessment of the data from a number of independently conducted studies.

2.3.3 Selection of relevant toxicity studies to assess potential carcinogenic risk

The ISO 10993-17 standard instructs the user to address carcinogenic as well as non-cancer risks posed by exposure of a patient to compounds released from medical device materials. There are no studies that have assessed the potential carcinogenicity of BPA in humans. The National Toxicology Program (NTP) conducted a two-year bioassay of BPA in mice and rats in which BPA was administered orally. Although a slight increase in the incidence of some tumor types was seen in rats following ingestion of large doses of BPA, the NTP concluded that none of the increases was attributed to BPA exposure.

More recently, studies have been published suggesting that parenteral exposure of experimental animals to BPA can result in pre-neoplastic changes in tissues. For example, Ho et al. (2006) reported that treatment of rats with BPA in a subcutaneous implant and 17β-estradiol/testosterone had an increased incidence of prostatic intraepithelial neoplasia (PIN), which is thought to be a precursor lesion to prostate cancer in humans. However, as pointed out by the CERHR expert panel, the human relevance of PIN in rodents is not clear. Also, no overt tumors were seen in this study. Newbold et al. (2007) observed an increased incidence of preneoplastic lesions in the uteri of mice 18 months after they received five subcutaneous injections of BPA; however, there was no dose-response seen and no overt tumors were observed.

Although no studies have shown an increased incidence of tumors in BPA-treated animals, the Ho et al., (2006) and Newbold et al. (2007) studies have called attention on the potential carcinogenic effects of BPA. Since this is a complex, cross-cutting issue, the FDA recommends that this issue be addressed on an Inter-Center basis to promote regulatory consistency across Centers.

2.4 Selection of Uncertainty Factors for TI derivation

Based on our preliminary review of the literature, CDRH does not believe that there is sufficient justification to depart from the default UFs used to account for interspecies differences in potency for BPA (UF1) or for interindividual variability in response to BPA in the human population (UF2).
As a result, the FDA is planning to use default values of 10 for each of the uncertainty factors, yielding an MF value of 100. However, as the Agency proceeds with the safety assessment, CDRH will carefully examine the available pharmacokinetic data on BPA to determine if compound-specific uncertainty factors can be derived.

A TI based on data from a 28-day toxicity study should be adequately protective for short-term exposure scenarios like cardiopulmonary bypass, but may not be sufficiently protective for long-term, repeated exposures that could occur in patients undergoing hemodialysis. If acute or subchronic toxicity data are used to derive the parenteral TI, CDRH will consider using an additional uncertainty factor to be adequately protective for long-term exposures.

2.5 Risk characterization

In the risk characterization step, the TI value for BPA is compared to doses of BPA received by patients undergoing various medical procedures. In addition, the uncertainties associated with estimation of dose and derivation of the TI are objectively and transparently identified.

2.5.1 Interpretation of dose/TI ratios

When assessing the significance of the dose/TI ratios, it is important to keep in mind that this comparison should not be viewed as a bright-line value, but rather as a general index of the safety. In other words, a dose/TI ratio ≤ 1 does not necessarily mean that a compound is "safe", nor does a dose/TI ≥ 1 indicate that adverse effects are likely in humans. Rather, these values should be used in a

relative sense to assess the likelihood that exposure to a compound will cause adverse effects in humans. Two other factors should be kept in mind as well when interpreting the significance of these values: 1) the TI is a value with uncertainty that spans perhaps an order of magnitude (Dourson et al., 1996), and 2) dose/TI ratios based on a comparison between short-term or one-time exposures (e.g. cardiopulmonary bypass) and a TI based on a repeat-dose toxicity study are likely to be conservative.

This information will be provided to risk managers to assist with regulatory decision-making regarding the safety of BPA-containing medical devices. Factors such as the relevance of the data for humans, uncertainties associated with the toxicity and exposure data, and any benefits conferred by the use of BPA in used in medical devices will be considered along with the dose/TI ratios values in making any regulatory decisions.

2.5.2 Uncertainties in exposure and toxicity assessment

Because of the assumptions that are necessary to estimate exposure and to evaluate the toxicity of a compound, there are a number of uncertainties present in any safety/risk assessment. These uncertainties will be clearly and transparently discussed in the safety assessment.

2.5.3 Alternatives to BPA

CDRH is currently evaluating whether alternatives exist to the use of BPA in medical device polymers and whether toxicity data exist for these compounds. It is important to keep in mind, however, that the clinical performance of the device may be altered by the use of alternatives. Clinically important risks associated with the use alternatives to BPA-containing polymers (e.g., changes in material characteristics or biocompatibility) may outweigh the theoretical risks of toxicity posed by patient exposure to BPA from these devices. The elimination of BPA as a constituent in polymers used in medical devices is a complex issue that warrants further study. Where alternatives are not already in place, any change would require significant safety studies to assess if such a replacement would pose new health risks.

The clinical relevance of this consideration should not be underappreciated. It is quite feasible that preliminary studies could identify alternatives that appear superior, yet a large scale shift to such a new product would add the significant risk of uncertainty, since clinical data would not exist. Conversely, if significant questions persist regarding BPA safety, then decisions/recommendations regarding alternatives could be based on pre-clinical toxicology study data. The Center also seeks input for the strategy relevant to adoption of new materials, for example, whether such materials should be introduced only in certain products or populations or with regulatory requirements for specific follow-up prior to permitting wide application of such material(s).

2.5.4 Protection of sensitive subpopulations

The results of experimental animal studies suggest that children and pregnant women may be more sensitive to the adverse effects of BPA than nonpregnant adults. The safety assessment will explicitly describe the extent to which the derived TI values are protective of sensitive subpopulations, such as children.

2.5.5 Tolerable Intake value vs. Allowable Limit value

The approach outlined in the 10993-17 standard instructs the user to initially calculate a science-based TI value. Other non-science factors, such as feasibility of achieving the TI and clinical benefit of the device, are taken into account when deriving an Allowable Limit for that compound released from a specific device. Consequently, this safety assessment will derive a Tolerable Intake for parenteral exposure to BPA, but will not necessarily derive an Allowable Limit for BPA released from specific

devices. Typically, it is only necessary to account for technical feasibility and device benefit only when the dose of the compound exceeds the TI.

3.0 How does the proposed CDRH/CBER/CDER approach compare to the approach used by Center for Food Safety and Applied Nutrition (CFSAN)?

The approach proposed by CDRH to conduct the safety assessment of BPA released from medical devices is conceptually similar to that used by CFSAN in their safety assessment. Both methods involve an estimation of the dose of BPA received by humans and a critical evaluation of the toxicity studies to identify a NOAEL/LOAEL or appropriate dose-response data for a BMD analysis. Unlike the CFSAN approach, CDRH will focus largely on the results of studies that employed dosing by parenteral routes of exposure. Another difference is that CDRH will derive TI values for BPA, whereas CFSAN used a "Margin of Safety" approach, comparing the NOAEL in a well-conducted animal study to the dose of BPA received by the general population.

5.0 Conclusions

This report summarizes the current focus of the Agency in the effort to understand the safety of BPA as a chemical component of medical products. FDA seeks the input of the Board to refine this initial set of investigations as well as guide the Agency for the subsequent studies that may be anticipated as relevant. This report does not serve as a complete or definitive assessment of BPA safety or utility, a goal that will be an ongoing target beyond this initial set of studies.

6.0 References

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