

Understanding the Public Health Impact of BPA in Medical Products

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February 24, 2009

Purpose of Today's Presentation

- Introduce the Science Board to the Agency's approach for understanding the public health impact of bisphenol-A in medical products
- Commit to the Science Board to circulate detailed Investigational Plan, with public disclosure, within the coming weeks
- Utilize today's meeting and your review of the Investigational Plan as opportunities for us to get feedback from you



The Importance of BPA

Examples include:

- BPA can have biologic activity modulating estrogen-dependent pathways
- BPA exposure could be of greatest concern in pediatric setting, particularly *in utero* and in prepubertal setting
- BPA exposure has been reported to be associated with a range of adverse clinical effects

BPA containing materials exist in medical products, particularly devices



Comparison of CFSAN and CDRH approaches

Food
(CFSAN - 2008)

- Focus on oral exposure studies
- Regulatory focus: safety assessment



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Medical Products (CDRH / CBER / CDER)

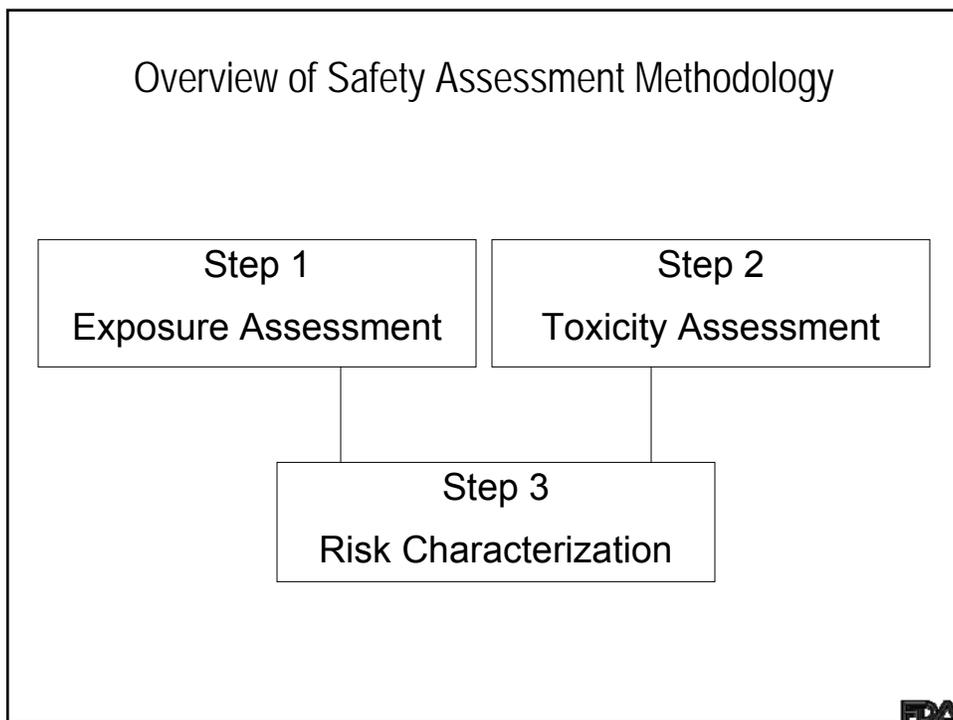
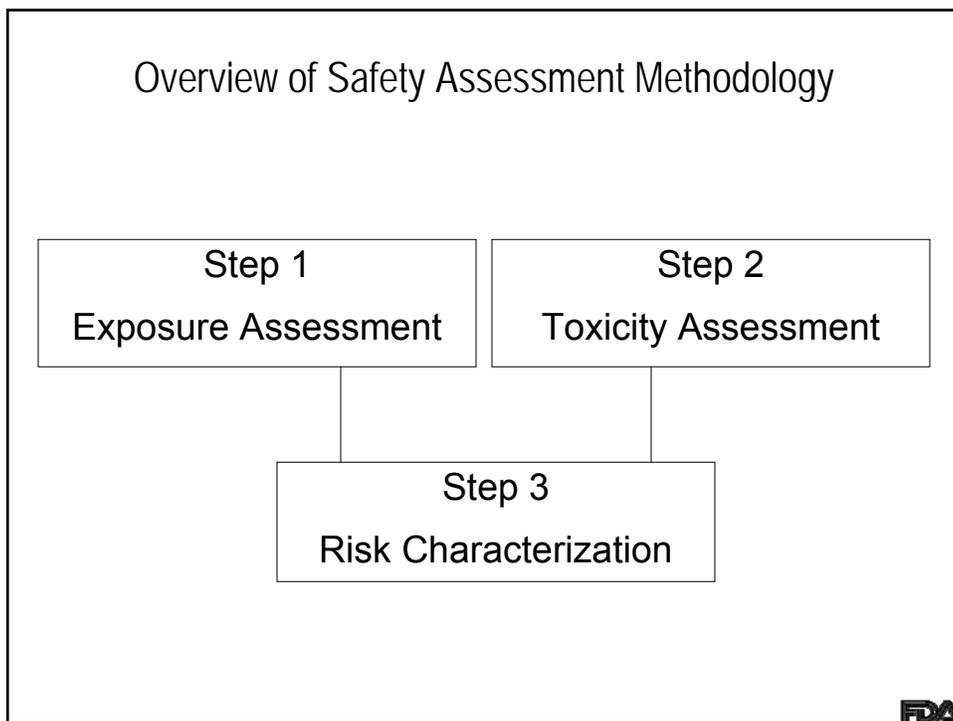
- Focus on parenteral exposure studies
- Regulatory focus: risk benefit assessment



Integrated Approach for Assessing Clinical Risk Associated with BPA as Component of Medical Products

1. Safety Assessment (CDRH/CDER/CBER)
 - Literature review
2. Data Gathering Efforts
 - Requested information via *Federal Register* notice
 - Quantify BPA exposure in patients
 - Evaluate alternatives to BPA





BPA is Contained Within a Wide Range of Medical Products

Examples include:

- Dental sealants
- Cardiopulmonary bypass circuits
- Hemodialysis circuits
- Containers for drugs & biologic agents



Performing Safety Assessment of Medical Products Must be Prioritized

- Effects of dental products:
 - The initial assessment is that exposure is very low relative to that from food, with transmucosal absorption at time of implantation brief and at low levels
- A proposal to identify exposure from all medical products is not practical. Thus, the initial focus is on products likely to be associated with higher exposures as well as susceptible populations



Safety Assessment Primarily Focuses on Devices That Allow Parenteral Exposure to BPA

- Direct blood contact to BPA-containing medical surfaces likely produce more extreme exposure
 - Potential for significant leaching
 - No first-pass hepatic metabolism
- Exposure from medical devices is amenable to study based on pharmacologic principles
- Even those medical devices likely to be associated with higher exposures to BPA have specific clinical benefits allowing estimation of net benefit



Proper Exposure Assessment Requires Steps to Reduce Uncertainty

Studies being initiated to measure exposure in specific settings to reduce uncertainty. CDRH collaborations initiated with:

- Children's National Medical Center and NCTR (cardiopulmonary bypass in children)
- University of Michigan (hemodialysis model circuit)



Clinical Investigations Provide Insight into Clinical Utility
By Focusing on Risk Relative to Benefit

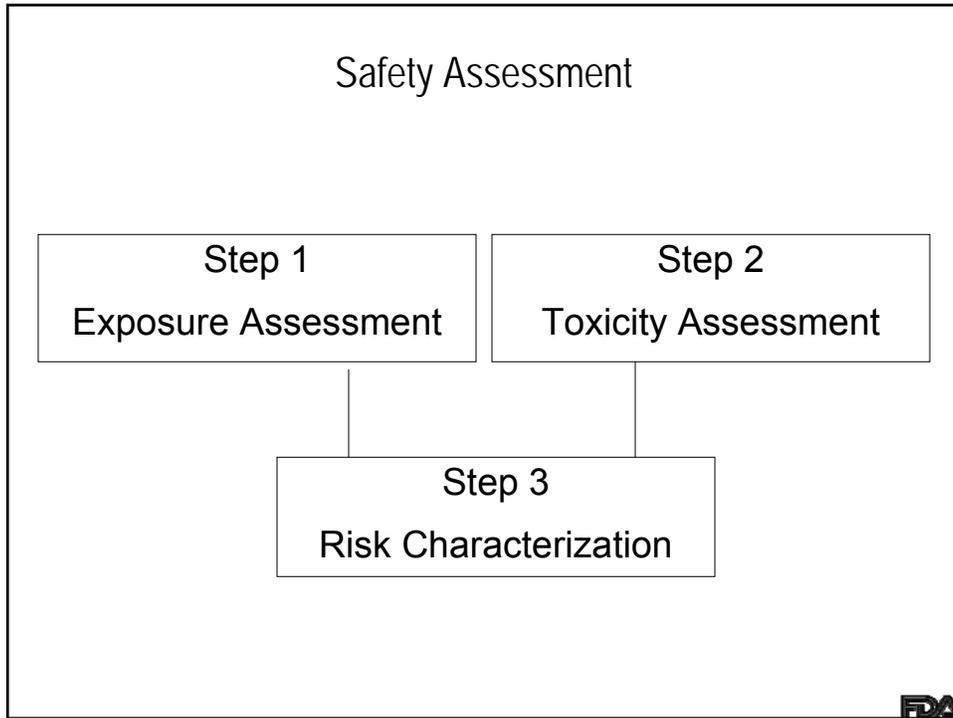
- Cardiopulmonary bypass is likely to permit a high systemic exposure to BPA via continuous direct blood contact for 2 hours or longer
- This “open heart” surgery is corrective
- Instead of dying as disabled kids, patients can reach adulthood without limitations
 - Public health view: clearly net benefit
 - CDRH investigating exposure in children

FDA

Clinical Investigations Provide Insight into Clinical Utility
By Focusing on Risk Relative to Benefit

- Hemodialysis is likely to permit a high systemic exposure to BPA via continuous direct blood contact for 4 hours repeated 3 times a week
- This renal-replacement therapy is life sustaining
- Instead of dying from kidney failure, patients survive with possibility of transplant
 - Public health view: clearly net benefit
 - CDRH investigating exposure in dialysis model

FDA



Determination of Tolerable Intake Required
for Toxicity Assessment As Defined by ISO-10993-17

- Agency proposes to adhere to this international consensus on how to conduct risk assessments for compounds released from medical devices
- Approach is conceptually similar to that used by CFSAN to derive ADI values and CDER to estimate first time drug dosages in humans
- This International Standard recommends accounting for both risk of BPA exposure and clinical benefit of using BPA-containing devices

Assessing Toxicity from Literature Review Preliminary Strategy

Studies to be Included

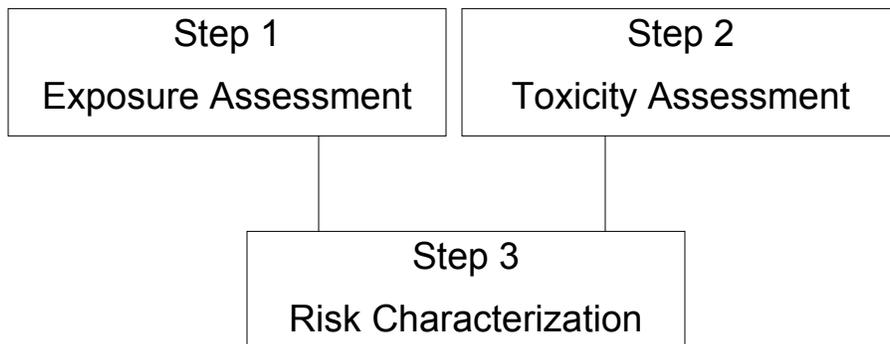
- Peer-reviewed publication
- Parenteral exposure
- Scientifically sound study
- Report of BPA purity not required
- Low phytoestrogen diet not required
- Single dose studies not necessarily excluded

Studies to be Considered

- Not published in peer-reviewed journal
- Oral route of exposure
- In vitro or pure PK studies
- Use of non-mammalian species
- Effects only seen at high doses (≥ 10 mg/kg/day)



Safety Assessment



The International Standards Help Frame the Risk Assessment for Medical Products

- Compare exposure (dose of BPA received by patients) to Tolerable Intake value
- International Standard includes transparency with regard to uncertainties in risk assessment
- Acceptability of BPA exposure to be determined on a case-by-case basis depending on:
 - clinical benefit of the device/drug
 - availability/clinical performance of alternatives
 - clinical status of the individual patient



Evaluation of BPA Alternatives

- Available information suggests several potential candidate replacements for BPA
- Very limited information on risk of these compounds
- Thus, these alternatives pose unknown risks and unclear effects on device function
 - CDRH initiating preliminary assessments of several candidates that could replace BPA, but these include brief exposure in preclinical settings



Net Clinical Benefit Is The Public Health Goal

- The Agency's goal is that medical products have minimized risk within the context of maximum potential benefits
- The Agency continues to focus on research internally and externally with this goal in mind
- We look forward to providing you with our Investigational Plan and receiving your feedback

