



## Meeting Report

# Predictive Alternative Methods for Assessing Biocompatibility of Dental Materials: A NIST-NIDCR Workshop Report

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Many promising new dental materials are being developed. One challenge in their commercialization is that their biocompatibility is often not tested until late in the product development cycle. If material scientists could identify biocompatibility related problems earlier in the design stages, this would enable them to change their processes or material components prior to investing significant resources into a material that would ultimately not pass regulatory testing. Therefore, early screening methods that are predictive of the dental material's biocompatibility would be of great benefit to the dental material developer community. The usage of these methods also has the potential to reduce animal testing and provide more rapid, human-relevant information.

The objectives of this workshop were to introduce quality tools to improve measurement confidence in alternative methods (e.g., *in vitro* or *in chemico* assays), learn about the Medical Device Development Tool (MDDT) process and how it can be applied to evaluate alternative methods for biocompatibility assessment, and build collaborations and share information among different stakeholder groups. A key goal of the workshop was to identify and prioritize opportunities for alternative methods for prediction of the biocompatibility of new dental materials to guide assay development in this area.

### Framework for alternative methods development

New approach methodologies (NAMs, e.g., *in vitro* or *in chemico* assays) have been increasingly developed and used in recent years to support regulatory evaluation of new products; it should be noted that the usage of the term “NAM” at the workshop and in this report differs from that in the FDA Center for Devices and Radiological Health's (CDRH's) MDDT program where NAM refers to non-clinical assessment model.<sup>1</sup> NAMs are typically designed to evaluate key molecular and cellular events that initiate adverse outcome pathways (AOPs) in mammalian systems (Ankley et al., 2010). There is a strong potential to develop NAMs for dental materials that are predictive of their biocompatibility and could be used for early screening in the dental materials process.

In an introductory presentation, Dr **John Elliott** (NIST) illustrated that it is critical for NAMs to have both good technical quality (robustness, reproducibility, etc.) and biological relevance (e.g., linkage to an AOP). If a NAM lacks either one of

these components, it is unlikely to be useful in the prediction of clinical outcomes of dental materials.

Drs **Elijah Petersen** and **Elliott** (NIST) gave subsequent presentations describing research strategies to assess the technical quality dimension of NAM development. Dr Petersen described a framework with key interrelated steps that aids in improving the technical quality during NAM development (Petersen et al., 2022a). The application of basic measurement quality tools (e.g., flow charts, cause-and-effect analysis, etc.) was illustrated with two assay use cases: an electrophilic allergen screening assay (designed for skin sensitization (Petersen et al., 2022b) and the MTS cytotoxicity test designed for use with nanomaterials (Elliott et al., 2017; Rösslein et al., 2015).

Dr **Nicole Kleinstreuer** (NIEHS) presented on the biological relevance dimension of NAM development. The usage of NAMs testing three key events in the AOP for skin sensitization, and their combination into “defined approaches,” was described. The Organization for Economic Cooperation and Development (OECD) has published guidance on how these NAMs can be used for regulatory decision-making (OECD, 2021), and the predictive capacity of these NAMs was shown through comparison to data from an *in vivo* method and with human reference data. These human biology-based defined approaches that integrate NAMs linked to the AOP-based key events provided better predictions of the human endpoint than the existing animal test methods. An example was also described for eye irritation/corrosion, and how NAMs developed for this endpoint could have superior biological relevance for humans, and better reproducibility, compared to an *in vivo* method using rabbits (Clippinger et al., 2021).

### Regulatory considerations

Drs **Edward Margerrison**, **Brittany Caldwell**, and **Simona Bancos** (FDA/CDRH) gave presentations related to key regulatory topics for biocompatibility testing of dental materials. Dr Margerrison presented several examples of alternative methods that could support medical device evaluation including photoacoustic imaging phantoms using tissue mimics (Hariri et al., 2021); a virtual family/population model for thermal, electromagnetic, and fluid dynamic simulations (Christ et al., 2010;

<sup>1</sup> Relevant websites include the following: <https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt>; <https://www.fda.gov/media/87134/download>; <https://www.fda.gov/media/109056/download>; <https://www.fda.gov/media/106994/download>



Gosselin et al., 2014; Iacono et al., 2015); and a color and hazard risk (CHRIS) calculator designed to help assess if the level of a color additive is likely to pose a biocompatibility concern (Saylor et al., 2019). Dr Caldwell presented general information about the MDDT program, including the benefits for qualifying tools, the types of MDDTs (clinical outcome assessments, biomarker tests, and nonclinical assessment models), details about what an MDDT is, how to access the list of MDDT qualified tools, and general information about the MDDT qualification process.<sup>1</sup> Qualified MDDTs are a set of methods that have been evaluated by FDA and can be used by sponsors within the qualified context of use, without the need to be re-evaluated in each submission, making the premarket process significantly more efficient. Dr Bancos described the general biocompatibility assessment approach of medical devices including when and how biocompatibility is considered,<sup>2</sup> considerations for qualification of test alternatives, and how to find consensus standards recognized fully or partially by FDA.<sup>3</sup>

#### *Advanced dental material development and clinical perspectives*

Drs **Carmem Pfeifer** (Oregon State University) and **Sharukh Khajotia** (University of Oklahoma) provided an academic perspective on dental materials development and biocompatibility testing. Dr Khajotia described the value of using standardized biocompatibility tests and a summary of the standards relevant for dental materials and associated FDA guidance. Limitations for performing biocompatibility tests by dental materials developers in academia (different expertise required, cost, time, etc.) and future needs were also described. He highlighted the tendency to test biocompatibility late rather than early in the product development process. Dr Pfeifer described the evaluation of new materials for dental fillings including measurements related to their physical and biological properties (e.g., cytotoxicity, enzymatic degradation) and long-term stability testing. Dr Pfeifer also described her experience in a U01 grant supported by NIDCR and what she learned about biocompatibility testing and dental material development.

#### *Meeting outcomes and lessons learned*

Many key aspects of the development of biocompatibility NAMs for dental materials were explored during the open discussions. One key point in developing NAMs that could be submitted to the MDDT process is that the context of use needs to be clearly described and specific as to how the tool helps assess device safety, effectiveness or performance. Acceptable performance criteria should also be provided. The need to raise awareness and for improved training about biocompatibility testing of dental materials with academic dental material scientists was also highlighted. Outreach and training could be proposed at key meetings (e.g., American Dental Association) attended by dental materials scientists.

#### *Future directions*

Challenges associated with testing extractables and leachables (E&L) were discussed. It will likely be necessary to test new dental materials using polar and nonpolar solvents, but many NAMs are not amenable to nonpolar solvents; the exception to this is NAMs that use 3D tissue constructs (De Jong et al., 2020).

Several new potential directions were identified for NAMs to support predictive biocompatibility testing of dental materials. One key research opportunity that emerged during the workshop was that screening methods developed in nanomedicine may have overlap with predictive biocompatibility testing of dental materials given that many novel dental materials use engineered nanomaterials (Sun et al., 2017; Padovani et al., 2015). Another key need was to evaluate to what extent NAMs that have a demonstrated use with dissolved chemicals can be used with polar, semipolar, and nonpolar extracts from medical devices (ISO, 2021a). A third key need that emerged during the workshop is for the development of an irritation test using oral mucosal 3D constructs that represent the oral environment. While a method has been developed for testing the irritation of medical devices for the skin, this method is not currently applicable for testing oral mucosal tissues (ISO, 2021b). Conducting further research and development in these areas will help advance predictive biocompatibility testing of new dental materials.

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<sup>2</sup> <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf>

<sup>3</sup> <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/Search.cfm>; <https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch>



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