MDDT Summary of Evidence and Basis of Qualification for Accelerated Testing to Prove Long Term Material Biostability

BACKGROUND

MDDT NAME: Accelerated Testing to Prove Long Term Material Biostability
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TOOL DESCRIPTION AND PRINCIPLE OF OPERATION

The tool measures the hydrolysis reaction rate of a thermoplastic polyurethane polymer when it is in a wet environment and establishes conditions under which the kinetics of the hydrolysis reaction can be accelerated for predicting long term performance in reasonable time frames. This tool augments the current guidance for new material introduction to long term implantable medical devices, where a dataset from a new material, implanted *in vivo* for two years without an oxidation challenge or for six months with an oxidative challenge, is extrapolated to modern day implant times of a decade or more to determine its suitability for use in a long-term medical device implant. (Appendix B: https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/submission-research-and-marketing-applications-permanent-pacemaker-leads-and-pacemaker-lead-adaptor).

Modern material science has led to the creation of materials with degradation rates too slow to be resolved over the timeframes historically utilized for new material evaluation. As such, this tool utilizes the well-established Arrhenius Equation to deduce acceleration factors that can be used to assess the reaction rate of a new material over implant times that are relevant to today's implant timeframes. This tool guides the user on how to age a material at higher temperatures and use this data to create a reduced time plot at body temperature. The method establishes a reaction rate, where data collected at higher temperatures can be used to validate the extrapolated body temperature data taken at short exposure times. As a result, a new material's stability can be more explicitly evaluated at long times without adding significant development time to the material stability work. In addition, the accelerated method allows for the evaluation of material properties at times nearer to the estimated end of life because it provides a recipe for creating aged samples in a short period of time. This makes it possible to evaluate the material performance of an aged sample under the loading conditions of the application resulting in a more explicit understanding about the probability of eventual material failure under the device use conditions.

The tool can be used at the material selection stage to determine if hydrolysis is a relevant degradation pathway for the material, enabling device developers to make an informed decision about designing a product with the material. Moreover, the tool allows the device comprised of the new material to be preconditioned to any hypothetical implant time and tested for its performance, giving critical insight to end of life device performance (e.g., abrasion for a lead application).

The tool addresses a critical gap in current preclinical testing, where biostability is only assessed over a timeframe of six months to two years of in vivo exposure. The absence of any signal of degradation over this abbreviated in vivo exposure results in a material being determined as biostable regardless of the intended service duration. This tool enables the hydrolytic degradation rate to be measured and scaled to the planned end of service, and the materials properties can be assessed for adequacy over the entire timeframe of use in the designed application.

CONTEXT OF USE

The Accelerated Testing to Prove Long Term Material Biostability tool is qualified to provide accelerated assessments of long-term hydrolytic stability for thermoplastic polyurethane materials used as insulation on cardiac and/or neuromodulation leads.

Accelerated Testing to Prove Long Term Material Biostability is specifically designed for materials intended to be biostable and implanted for long times in the body (>10 years), where the rate of reaction is hard to distinguish at short implant times typical of pre-clinical in vivo exposures because the signal of the reaction is within the typical experimental noise of the measurement system (i.e., molar mass can only be reliably assessed to within +/- 10%). This tool measures the hydrolytic reaction rate at multiple temperatures carried out at atmospheric pressure in a neutrally buffered (pH~7) saline solution at physiological concentrations where the backbone reactions are monitored with GPC/SEC. The measured reaction rates are then used to establish the temperature dependent acceleration factors using the Arrhenius relationship, which can be used to scale accelerated, high temperature exposures to predict real-time performance at physiological temperature.

This tool is not designed for material process monitoring or assessing lot-to-lot variation. While the tool does not address the specific nature of the chemical reaction that occurs (i.e. the chemistry) during hydrolysis, it does give a ‘recipe’ for degrading the material to the point that NMR (Nuclear Magnetic Resonance) Spectroscopy can be effective at identifying the specific hydrolysis chemistry.

SUMMARY OF EVIDENCE TO SUPPORT QUALIFICATION

The tool will provide quantitative metrics of the hydrolytic rate of chemical reaction over the entire lifetime of the implanted material. The rate of the hydrolysis reaction is accelerated with temperature according to the long-standing Arrhenius equation and

both the rate of chemical reaction and the activation energy are measured. This contrasts with the current standard which relies on qualitative metrics focused on comparisons (i.e., surface cracking) with a comparator material known to perform well. The current approach, which assesses performance with respect to a comparator material when exposed to an oxidative challenge condition, assumes an unchanged activation energy for the materials being compared, a case that is only true when the same bonds are impacted by the reaction. In this tool, the number of relevant polymer backbone reactions are counted as a function of time. The method allows for different materials to have different activation energies, allowing the reaction rate of unlike materials to be quantitatively compared to a comparator material (see Figure 7, Macromolecules 2014).

The pre-clinical (*in vivo* animal) response has extremely high variation due to the variability between animals and the low number of replicates. We have analyzed two materials (PDMS-urethane and carbonate-urethane) and in both cases, we see that the accelerated prediction is in good agreement with the pre-clinical response.

Criteria:

1. Conduct real time *in vivo* testing and compare to accelerated *in vitro* exposures and demonstrate that extrapolation to 10-years results in a molar mass distribution that is indistinguishable. (Column 3 vs column 4 in table directly below) NOTE*: We typically extend our pre-clinical exposures beyond those required in the standard due to the inability of the short, required times to reveal a reaction that could be relevant in modern day implant durations if it exists.*
2. Evaluate the molar mass of the explanted materials and confirm that the accelerated tests are consistent with the *in vivo* results. Expect the *in vivo* results to have high variation due to the limited number of analysis points as compared to the accelerated *in vitro* predictive testing.
3. The statistical comparison shall be performed with a 95% prediction limits. Over lapping limits between the real time and the accelerated tests shall serve as validation.

The datasets compared demonstrate that the tool neither overestimates nor underestimates the rate of *in vivo* hydrolysis. The molar mass, used to evaluate the extent of reaction, must change by more than 10% for modern size exclusion chromatography (SEC) instrumentation to definitively determine a change in the molar mass, especially when repeated measurements are accrued over time for the analysis.

Five materials were evaluated *in vivo* (20-year human, 5-year sheep, 2-year rabbit), where this data was compared to long term *in vitro* real time testing at body temperature (ranging in testing duration from 1-10 years), and *in vitro* accelerated testing (ranging in testing duration from 1-5 years). These data are tabulated in Table 1, where the 10-year molar mass estimate for all datasets is practically indistinguishable given the variance of modern-day SEC techniques. More importantly, the *in vivo* implant duration required to resolve the hydrolysis reaction exceeded the current guidance for all materials

evaluated, indicating that none of these materials would have been flagged as having changing properties over the duration of the implant using the current guidelines (see column labeled 5 and highlighted in blue). Given the number of years indicated in column 5, it is clear that historical implant durations of 2-3 years did not introduce an error into the assessment of a material's stability because changes in the molar mass could not be resolved. However, today, the implant time required to resolve a material change lies within timeframes that are relevant to modern day implants, revealing a gap that must be closed in the analysis of biostability with respect to today's longevity requirements.

Summary of example materials and their predicted molar mass at 10 years. The range was calculated from the Upper and Lower Confidence bounds.

Material	(1) Initial Molar mass[a] Mn(t=0) (kDaltons)	(2) In vivo Exposure Molar Mass Range @10 yrs (kDaltons) LCB-UCB (study duration)	(3) Real Time Age (*in vitro*) Molar Mass Range @ 10 yrs (kDaltons) LCB-UCB (study duration)	(4) Accelerated Testing (in vitro) Molar Mass Range @10 yrs (kDaltons) LCB-UCB (study duration)	(5) Implant time required in vivo to resolve degradation (years) ($M_n(0)/(M_n(t)=1.1$	P-value (Molar mass indistinguishable) Reference accelerated data (same as animal model)
Optim™ PDMS-PU	48	17-25 (5 year sheep)	22-25 (10 years)	19-22 (1 year)	3.8	<0.0001
Bionate™ 80A	73	46-58 (5 year sheep)	40-65 (5 years)	40-67 (5 years)	6.1	<0.0001
PEU80A	160	114-no change (20 year human)	No change (1 year)	115-no change (1 year)	30	<0.0001
Quadrasil™	55	21-42 (5 year sheep)	19-no change (5 years)	14-42 (5 years)	7.7	<0.0001
Carbothane™	41	No change (2 year rabbit)	35-no change (3 years)	27-35 (3 years)	8.0	<0.0001

[a] Uncertainty in M_n is ~10% and molar mass was absolute

ASSESSMENT OF THE ADVANTAGES AND DISADVANTAGES OF QUALIFICATION

The tool has the advantage of being able to resolve a relevant material degradation reaction within timeframes that are consistent with the product development timeframes, preventing a material being assessed as stable when it will in fact degrade over a time horizon that is relevant to the device performance objectives. The second advantage of this tool is that it allows for a material to be taken to an extent of reaction that is consistent with the planned end of device timeframe, then evaluated for its performance at end-of-life. This is attractive as device implant durations continue to expand, allowing for the introduction of product surveillance and proactive replacement, ensuring the continued high reliability of implantable medical devices.

The tool has the disadvantage of not being able to quantitatively predict con-current reactions (e.g., hydrolysis and oxidation) and therefore could underestimate the extent of *in vivo* reaction resulting in a material that would fail earlier in time than predicted if oxidative degradation was a significant degradation pathway. In our demonstration materials, we specifically picked materials that had improved oxidative performance and should have been selected as having improved biostability over poly(ether)urethane according to the current guidance (i.e., focused on the oxidative challenge). This is the reason that the table above shows good agreement between columns 2, 3, and 4. If oxidation were a significant contributor, its superficial nature would not be adequately captured by molar mass when the entire bulk cross section was utilized in the analysis. If oxidation was in the form of MIO (metal induced oxidation), then the bulk molar mass would drop and column 2 would have a lower molar mass than column 3 and 4.

CONCLUSION

New material introduction to an implanted pacemaker or defibrillator leads is more difficult today than ever before. Improved battery technology and energy efficient circuit designs have increased device longevity and following that lead longevity exponentially over the last two decades. When devices had longevities comparable to the length of the development cycle, material stability and performance was evaluated in real time throughout the research and technology phases, meeting up with the product development phase before launch. Instabilities were either recognized or their rates were sufficiently slow such that devices reached end of life before the changing materials properties impacted performance. Today, cardiac and neuromodulation leads are expected to last at a minimum of 15 years, where next generation leads have longevity targets of 20 years or longer. As a result, a new material should be expected to change over time, where the rate of change is understood and the consequence of this change on device performance has been assessed. This tool is an important addition to the guidance for the creation of new devices with these modern-day longevity expectations, while still maintaining the high reliability that is essential in the medical device industry.

This tool fills a critical gap in the current guidance for introducing a new material into the long-term implanted space for applications like the primary insulation on cardiac and neuromodulation leads, where hydrolysis is not explicitly evaluated as an *in vivo*

degradation reaction. This tool teaches how to isolate the hydrolysis reaction and monitor its rate at the service temperature and a series of higher temperatures. Finally, it instructs on the proper method for applying the Arrhenius Equation to create a reduced time plot which allows the reaction kinetics to be assessed over periods of time that exceed those evaluated with real time testing. Furthermore, this tool provides a recipe for accelerating the chemical degradation to the anticipated end-of-life time duration, allowing for device performance to be evaluated after the material properties change over the extended implantation times that are demanded with modern implanted device therapies.

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