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Veranex
Biocompatibility Coffee Break

AGING WITH GRACE: KEY DISCUSSION POINTS ON END-OF-LIFE ASSESSMENT

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This whitepaper is a result of a discussion led by the authors as part of Veranex's Biocompatibility Coffee Break[1] in February 2024. It includes the critical industry questions that arose during the discussion.

Introduction

End-of-life assessment is still a relatively unexplored field with limited guidance on the right approach. This discussion centers around appropriate and scientifically relevant methods used to test or establish a safety profile for the reusable medical devices and how to best set up an evaluation to address the potential added risks from reprocessing medical devices until their point of decommission.

The Number of Cycles

For reprocessed devices ISO 10993-1 recommends biological safety be assessed for the maximum validated processing cycles. However, this can be hundreds of cycles. Does it really make sense to run all those cycles to answer the question of biocompatibility over the whole life cycle? In many cases the IFU also mentions conditions that would take the device out of commission before its maximum validated cycle number is reached. Also many reusable devices do not have a maximum validated cycle number but can be used for hundreds of cycles, maybe even more than a similar device from another company that has set a maximum number for their product. We believe these should be evaluated by following the same general concept.

Thus, instead of reprocessing devices to their maximum life cycle, we propose an approach where a trendline is established and appropriate markers are used to demonstrate whether there is an indication of concerning changes happening that could impact the biocompatibility profile of the device. And perhaps a single study can be designed to address concerns from both reprocessing (e.g., functionality) and biocompatibility (e.g., material changes, residual buildup) sides.

Based on the discussion from the coffee break session, it is evident that many different strategies have been utilized to determine the appropriate number of cycles. For instance, a common approach includes 6 cycles, which originates from AAMI ST98, a guideline for cleaning validations of reusable medical devices. Based on the comments during the discussion, success with both FDA and TÜV has also been achieved with 10 reprocessed cycles and high-level chemistry markers, such as total organic carbon (TOC) and non-volatile residue (NVR) assessment. While it is great to hear these success stories, there is still so much ambiguity on the topic and, due to lack of guidance from standards, it can lead to different expectations from different regulatory reviewers. Furthermore, knowing that the device can potentially be reprocessed for hundreds of cycles, perhaps having a single datapoint at 10 cycles and combining it with the baseline assessment at first-time use condition, is not quite enough. That is why

establishing a trendline instead may provide a more wholesome picture of the impact of reprocessing on the device. When the approach of a trendline over the course of the whole life cycle is used, typically at least a couple of cycle points should be considered. For instance, we recommend an assessment of relevant markers after 10, 25, and 50 cycles and a comparison of these to the results obtained from the device condition at baseline (i.e. representative of first-time use condition). It should be noted that the number of chosen representative cycles can strongly depend on the number of devices available for testing. In addition, the number of representative cycle points may be different depending on the materials used for the device (e.g., whether it is completely metallic or made of polymeric resins). The impact of reprocessing on polymeric materials is much less known than for metallic devices, and polymeric materials are in general known to be more impacted by reprocessing.

Additional reinforcement for better definition of the "conditions" when a device should be taken out of commission was noted by some of the comments. Currently, a couple common IFU statements are "observation of rusting" and "visual damage." These are more easily notable for metal devices compared to non-metal devices. However, it might be a good idea for the manufacturers to also consider notes for devices with polymeric materials, especially if it is known which parts of the device contain the polymeric materials and how they can be most impacted by the reprocessing cycles and repeated handling.

Also, whenever possible, it is always a good idea to discuss the proposed approach with your regulatory reviewer(s) in order to align the expectations before commencing this resource-heavy study.

Considerations for Cycle Parameters

When considering how to best mimic the aging process, one should take into account the conditions recommended in the specific IFU or real-world evidence (e.g., what is actually done in the hospital reprocessing centers). The idea behind assessing the impact of reprocessing is to make sure that the devices included in the assessment truly represent those to which the patient could potentially be exposed.

For reusable devices the chemicals as well as the temperatures that are faced during the reprocessing cycles should be considered. Detergents as well as disinfectants can not only accumulate on the surface of the device over time but can also impact the materials of construction by changing their chemistry or making them more brittle, resulting in more wear and the potential formation of hazardous particulates that were not assessed with the biocompatibility evaluation performed at the first-time-use state of the device. Heating during cleaning cycles can also cause some additives within the polymeric material to migrate to the surface and be exposed to the patient during use; these changes in the materials may not be adequately captured when testing only the first-time use device state. As such, building the reprocessing cycles to capture these potential impacts is key to the assessment.

Defining the appropriate reprocessing cycles to be used for the whole life-cycle analysis can be tricky when an IFU allows multiple pathways for the user, including sterilization and disinfection as well as different types of cleaning agents (alkaline vs enzymatic). As all these can impact the materials of the device, it may be worth combining them into the representative reprocessing cycle rather than perform multiple separate studies.

We want to note that sometimes a so-called standard cycle can be recommended instead of the device-specific IFU for these cycles[2]. The standard cycle is set up based on cycles that are commonly used in a hospital reprocessing centers and, thus, follow more closely what happens in the real world in terms of reprocessing. This approach may serve also as a reduction in time to perform the reprocessing cycles, as it presents a more uniform and simpler cycle-parameter selection for the lab personnel.

Appropriate Analytical Tests as Markers

The choice of analytical tests that could be used as s-called markers for evaluation is another key factor in designing a study that addresses the concerns of reprocessing over the course of the whole life cycle of the reprocessed device. As discussed in the coffee break session, there are a number of aspects that should be considered when addressing the impact of reprocessing to the device and, therefore, to the exposure to patients, including the potential of chemical (e.g., detergents and disinfectants) buildup on the device due to accumulation on/in hard-to-reach areas, changes to the material-extractables profile, and any potential wear that could lead to brittleness and particulates.

The framework of how to address potential residual buildup, including reprocessing chemicals, can be found in AAMI ST98. This framework can also be adjusted to address this aspect for residual buildup over the course of reprocessing. According to AAMI ST98, TOC testing (conducted per USP<643>) is an analytical method that is widely used as a marker for presence of detergents in pharmaceutical manufacturing equipment, cleaned single-use devices, and cleaned reusable devices. While TOC analysis is not expected to provide identities of residues, its use here is more targeted toward establishing a trendline over the different chosen number of reprocessing cycles as timepoints. As such, it can be seen as a robust approach to address residual buildup.

It should, however, be noted that knowledge of chemicals used and the assay that would be best to detect their presence is needed in order to target the specific residuals. For instance, when enzymatic detergents are recommended for use in reprocessing, a protein analysis, instead of TOC, may be a better option. Also, many disinfectants are not carbon-based, and, therefore, a more relevant test method as marker should be considered.

To understand and evaluate any potential changes to the materials of constructions, a step-wise approach may be considered. As a first step, a visual inspection after the chosen representative cycles should be conducted. This will help to determine whether there are notable changes to the device after reprocessing. These notable changes should include a general functionality check of the device, rusting on metal components, any color change, noticeable wear, particulates, etc. These are good indicators that there is a change happening that could potentially impact the biocompatibility of the device. The downside to this is that it is a qualitative marker and may not provide the whole story about the changes.

Another suggested quantitative general marker for evaluating any changes, including wear, is the Non-Volatile Residues (NVR) method. As noted in ISO 10993-18, NVR as a general method can provide estimates of the total amount of extracted substances; while not providing any information on the identities of the extractables nor their specific concentrations, it might provide a high-level idea of whether an increase in leachables, as well as shedding of particulates, is occurring over the course of multiple reprocessing cycles.

In addition, cytotoxicity testing, as the cornerstone of biocompatibility tests often used for screening purposes, may be considered. This is especially useful for devices that have demonstrated a low cytotoxic reactivity at the first-time-use condition. In those cases, demonstrating that repeat cycles do not increase cytotoxic potential is a great way to address the overall condition of the device after reprocessing, including any residuals as well as extractables from the materials. The cytotoxicity test, however, carries some known drawbacks, such as reactivity against certain materials or chemicals. For instance, when a disinfectant is used, it is fairly common that even small amounts of these chemical products can impact the result of this test due to the fact these disinfectants are intended to kill cells. Also, in cases where the device in its first-time-use condition has demonstrated cytotoxic potential, this may not be the best marker for evaluating changes.

Acceptance Criteria

The concept of marker testing is recommended, wherever possible, to avoid performing additional rounds of full biocompatibility testing on devices over their whole life cycle, especially unnecessary animal testing as well as extensive resource-expensive analytical chemistry testing per ISO 10993-18. Obviously, where marker testing defines problems that may require additional testing, the commencement of investigation into specific risks and the most appropriate ways to address them is appropriate.

When you are addressing the concern of residual buildup, the evaluation of the trendline, rather than specific acceptable amounts, should be considered. This is because the biocompatibility profile for the device will have already been established for the first-time-use condition of the device using the concepts of ISO 10993-1, and the point of the marker trend analysis is to evaluate whether there are additional concerns for the device that were not previously addressed. Where data from chosen reprocessing cycles demonstrate no trend in residual buildup or impact to materials, the evaluation of whole life cycle should be considered as complete.

Summary

All in all the aim of this discussion was to focus the evaluation of end of life on using a risk-based approach and to help better define the risks that reprocessing could potentially have for a medical device. We continue to shape the approach based on input from the industry to develop a scientifically justified and more uniform approach to perform this assessment in order to help align the expectations from both the regulators and the manufacturers.

References

1. Veranex Biocompatibility. (n.d.). Home [LinkedIn page]. LinkedIn. Retrieved May 10, 2024, from https://www.linkedin.com/company/veranexbiocompatibility/

2. Patel, A. & Barber, B. (2024, April 25). A New Approach to End-of-Life Testing. Nelson Labs. https://www.nelsonlabs.com/a-new-approach-to-end-of-life-testing/