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Calytra Insights #2: Rapid Early Feasibility Study (EFS) Strategy

1.0 Purpose:

This document outlines a streamlined strategy for conducting an Early Feasibility Study (EFS) utilizing hand-carry logistics, packaging validation, and lot release sterilization. The approach minimizes regulatory hurdles and expedites the process by focusing on essential validation steps while eliminating aging studies. The purpose is to provide a structured framework that ensures compliance with regulatory requirements while maintaining efficiency in cost and time.

2.0 Scope:

This document applies to medical device developers and regulatory teams seeking an accelerated EFS approval pathway. It covers key regulatory considerations, testing requirements, estimated costs, and potential risks. The scope includes pre-submission discussions with the FDA, validation of packaging and sterilization processes, and functional product testing necessary to support device integrity throughout the study period.

3.0 Insight Summary

This strategy accelerates an Early Feasibility Study (EFS) by leveraging hand-carry logistics, packaging validation, and lot release sterilization. Aging studies are excluded, and product shelf life is limited to six months post-sterilization based on accepted pre-sub communication. The goal is to streamline regulatory approval and minimize pre-clinical testing delays. The document details critical components such as regulatory interactions, sterilization robustness, and functional product testing, along with a breakdown of biocompatibility requirements and potential challenges associated with the approach.

3.1. Rapid EFS Strategy

Pre-Sub Meetings with FDA: Engage in pre-submission discussions with the FDA to confirm amenability to the hand-carry approach and document regulatory expectations. This is a common strategy for an EFS, but it is important to engage with the FDA early and often through the Q-sub process. A summary of the rapid EFS strategy is described in ***Table 1***

Table 1: Rapid EFS Strategy

Ref	Challenge	Change
1	Hand Carry	Devices are transported directly to clinical sites which will avoid the requirement to validate the distribution process.
2	Sealing Validation	Sealing process validated per ASTM F88/F2096 to ensure sterility.
3	Single Lot Release	Ethylene oxide (EO) sterilization per ISO 11135:2014 Annex E, utilizing half-cycle and full-cycle validation.

Ref	Challenge	Change
4	No AA testing	Shelf life is based on prior references, pre-clinical studies, and justifications of material properties and history of use rather than accelerated aging tests, reducing upfront verification work.
5	Functional Testing	Functional testing post-sterilization to ensure device integrity and usability, including ISO 10993 biocompatibility assessments.

Regulatory and Testing Requirements

To ensure compliance with FDA and international regulatory standards, testing must adhere to the following:

3.1.1. ISO 11135:2014 Annex E- Single Lot Release

ISO 11135:2014 Annex E establishes detailed requirements for the validation and routine control of EO sterilization to ensure effectiveness and reproducibility. Bioburden testing must be performed pre-sterilization to quantify microbial load, ensuring sterility assurance levels (SAL) are met. The EO sterilization process should follow a structured approach incorporating fractional cycles to determine process efficacy and establish worst-case sterilization conditions.

The validation process includes executing a half-cycle exposure followed by a full-cycle to confirm the process achieves the required sterility assurance level after each cycle while maintaining compliance with ISO 10993-7 residual limits. Internal process challenge devices (iPCDs) must be strategically placed within the sterilization load to assess the most challenging sterilization conditions and confirm process effectiveness. The sterilization process is considered validated only if all test microorganisms from the iPCDs exposed to the fractional and full cycle demonstrate no viable growth post-exposure and naïve product sterility testing demonstrates no viable growth.

3.1.1.1. Functional Testing

The standard requires that manufacturers document and successfully complete product functionality testing to confirm that the sterilization cycle does not negatively impact the intended use of the product. Testing will demonstrate that the critical functions of the device remain intact immediately after sterilization (e.g., usability, operational performance).

There are several options for the type of sterilization cycle used for product functionality testing. A 2x sterilization cycle can be used to represent the worst-case processing condition. This will demonstrate the product functionality relative to the lot release approach described above as per Annex E of ISO 11135:2014 (1.5x sterilization cycle), as well as future sterilization cycles which may require reprocessing (2x sterilization cycle).

3.1.2. ASTM F88/F88M - Seal Strength Testing

ASTM F88/F88M defines the process for measuring package seal strength to confirm the sterile barrier's integrity. Seal strength must exceed the minimum force threshold to prevent

contamination during transport and storage. The testing is conducted under tensile conditions, and failure modes must be documented to ensure consistent quality. The process includes testing at both minimum and maximum sealing parameters during operational and performance qualification phases.

3.1.3. ASTM F2096 - Bubble Leak Testing

ASTM F2096 outlines the bubble leak test methodology used to detect leaks in sterile barrier systems. This test applies internal air pressure to submerged packages to identify the presence of leaks. According to the standard, packages must not exhibit any continuous or intermittent stream of bubbles under test conditions. The method serves as a non-destructive approach to confirming package integrity before and after sterilization. A minimum of 29 samples per batch must be tested in accordance with regulatory best practices.

3.1.4. ISO 10993 - Biocompatibility Testing

ISO 10993 biocompatibility testing ensures medical devices do not cause adverse biological reactions. This testing is generally considered mandatory, however the standard makes clear that certain testing may not be appropriate provided a risk analysis has determined that the testing would offer no additional benefit or risk mitigation. This may be based on the material's historied use in the field, prior chemical characterizations which would be applicable, or evidence from pre-clinical testing.

Biocompatibility testing includes cytotoxicity, sensitization, and irritation among other assessments to confirm patient safety. Testing is often conducted under worst-case conditions, taking into consideration multiple sterilization cycles when applicable. Testing may also be conducted on representative samples in cases where practical challenges prevent meeting explicit requirements for surface area or volume defined in the standards. Depending on your pre-clinical work, and your relationship with the FDA through pre-sub discussions, it's not uncommon for the FDA to intimate their willingness to accept justifications in lieu of testing, particularly for genotoxicity, carcinogenicity, and systemic toxicity.

Table 2 outlines the required biocompatibility tests based on device type, tissue contact, and contact duration as per ISO 10993-1:2009(E):

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Table 2: ISO 10993-1:2009(E) Annex A

Evaluation tests for consideration

Category	Contact	Contact Duration A: ≤24h; B: 24h-30d; C:>30d	Cytotoxicity	Sensitization	Irritation/Intracutaneous Reactivity	Systemic Toxicity (Acute)	Subchronic Toxicity	Genotoxicity	Implantation	Haemocompatibility
Surface device	Skin	A	■		■					
		B	■	■	■					
		C	■	■	■					
	Mucosal membrane	A	■	■	■					
		B	■	■	■					
		C	■	■	■					
	Breached or compromised surface	A	■	■	■	■				
		B	■	■	■	■				
		C	■	■	■	■				
External communicating device	Blood path, indirect	A	■	■	■	■				■
		B	■	■	■	■				■
		C	■	■	■	■	■			■
	Tissue Bone Dentin	A	■	■	■	■				■
		B	■	■	■	■	■			■
		C	■	■	■	■	■			■
	Circulating blood	A	■	■	■	■	■	■	■	■
		B	■	■	■	■	■	■	■	■
		C	■	■	■	■	■	■	■	■
Implant device	Tissue Bone	A	■	■	■	■	■			■
		B	■	■	■	■	■			■
		C	■	■	■	■	■			■
	Blood	A	■	■	■	■	■	■	■	■
		B	■	■	■	■	■	■	■	■
		C	■	■	■	■	■	■	■	■

3.1.5. Challenges

While this strategy offers significant advantages in terms of speed and cost reduction, it presents several distinct challenges. One of the primary concerns is the robustness of the device to repeated sterilization cycles. If a product cannot withstand at least 1.5x sterilization cycles without degradation, additional validation testing will be required, increasing costs and time to trial.

Another challenge is the logistical complexity of manufacturing and sterilizing devices every 3-6 months. Since aging studies are not conducted, frequent production runs are necessary to allow timely enrollment given the short shelf-life. This may pose additional challenges related to supply chain management and internal manufacturing lead times. Additionally, reliance on hand-carry logistics may not be scalable given the complexity of the clinical effort and scope. A production sterilization validation will eventually be required, so the strategy adds cost at the benefit of reducing time to trial.

4.0 Conclusion

The approach described herein is ideal for rapidly initiating an EFS but comes with trade-offs. It is most effective when the device is robust to sterilization and has a clear path to clinical use without extended shelf-life validation. Careful planning is required to manage production schedules and supply chains, however simulated distribution, shelf life testing, and/or sterilization validation can completed at any time along the path along to alleviate any manufacturing pressure that arises.