U.S. FOOD & DRUG ADMINISTRATION

Evaluation of Device Performance for Labeled Shelf Life

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Webinar for Device Stability

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Outline of Presentation

I. Shelf Life and Stability of a Medical Device

II. Product Shelf Life Testing

III. Recommendations for Product Shelf Life Testing – Examples

- Joint Arthroplasty Devices
- Resorbable Bone Void Filler Devices
- Patient-Matched Instruments to Orthopedic Implants
- Other Devices

*Disclaimers

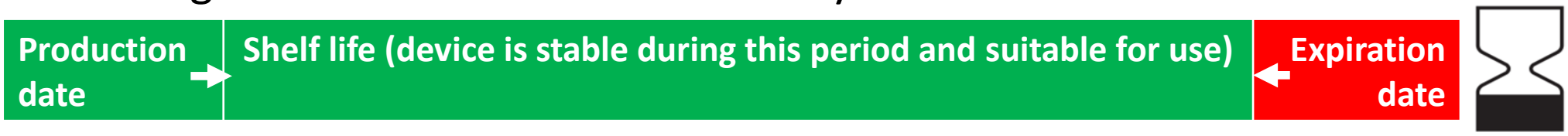
- Language from FDA guidance documents has been excerpted or summarized to fit the purpose of this presentation. For complete information, please review the cited FDA guidance documents.
- Our recommendations in this presentation are based on our current thinking on a particular subject, which may be subject to change.
- Images have been obtained from online sources and are intended for illustration only.

Shelf Life and Stability of a Medical Device

FDA guidance - Shelf Life of Medical Devices April 1991
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/shelf-life-medical-devices

Shelf Life of a Medical Device - Terminology

- Shelf life is the term or period during which a medical device remains stable and suitable for the intended use.
- An expiration date is the termination of shelf life, after which a percentage of the medical devices may no longer function as intended.
- Not all medical devices need to have a shelf life; this depends if a medical device is susceptible to degradation that would lead to functional failure and the level of risk that the failure would present.
- A medical device's shelf life should not be confused with its "useful life" which is the duration of actual use or the number and duration of repeat uses before some change results in the device's inability to achieve its intended function.



Stability and Stability Criteria

- The United States Pharmacopoeia (USP) defines stability as "the extent to which a product retains, within specified limits, and throughout its period of storage and use, i.e., its shelf life, the same properties and characteristics that it possessed at the time of manufacture."

- There is no one exhaustive set of criteria that would apply equally to all medical devices. USP section <1191> provides five sets of **criteria** for acceptable levels of stability for **drug products:**
    1. chemical
    2. physical
    3. microbiological
    4. therapeutic
    5. toxicological
    6. biocompatibility (**added for medical devices**)

- This is the starting point for developing criteria to evaluate the stability of medical devices.

Factors to Consider for Each Stability Criterion - Examples

Chemical

- **Degradation** of ingredients or components
- **Interactions** of ingredients or components or between device and packaging
- **Manufacturing** that alters the chemistry of materials or components
- **Radioactive decay**

Physical

- **Physical characteristics**, e.g., appearance, viscosity, mechanical properties
- **Manufacturing** that affects the physical characteristics
- **Storage (including transport) conditions**, e.g., temperature, humidity, light, vibration

Microbiological

- **Sterility/integrity,** i.e., package integrity
- **Environmental control**
- **Antimicrobial effectiveness**
- **Preservative effectiveness**

Therapeutic: impact of storage or use conditions on intended therapeutic or diagnostic function

Toxicological: formation of device degradation by-products during storage or use that produce an adverse toxic effect

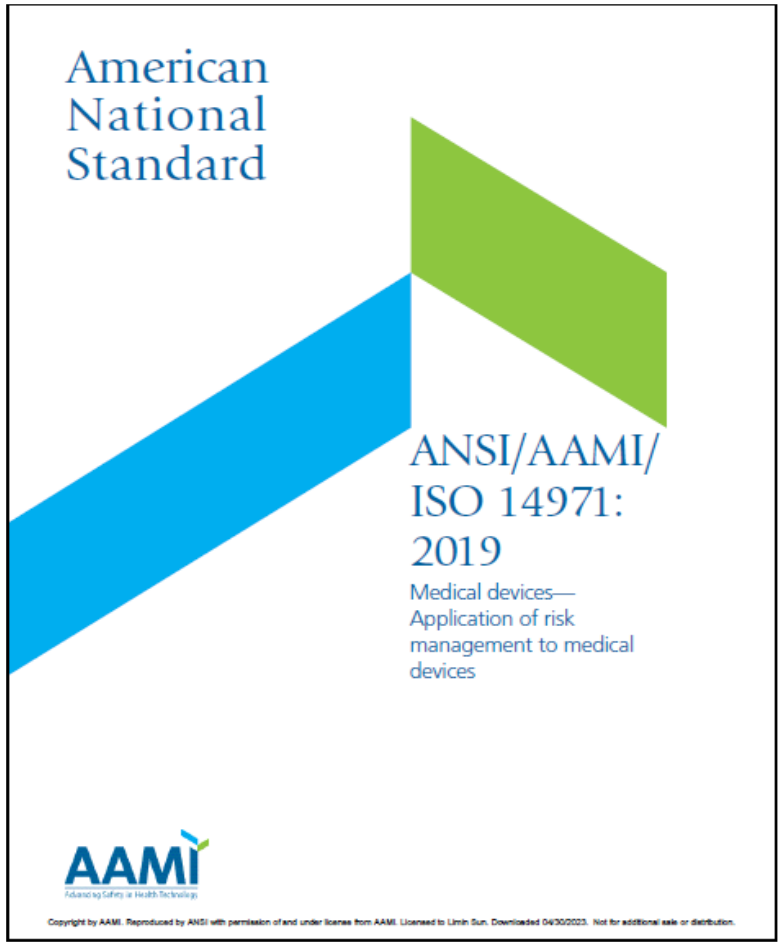
Biocompatibility: potential adverse effects on biocompatibility due to storage or use

Note that the above factors are device-specific!

Risk Analysis

It is recommended to perform a risk analysis that

- is in accordance with the currently FDA recognized version of ANSI/AAMI/ISO 14971 for all stability factors to determine if and what shelf life testing is needed
- is specific to the medical device type with consideration to
  - nature of the device and intended use
  - materials and components used to manufacture the device
  - manufacture method and process (including sterilization)
  - packaging, storage and transportation conditions



Product Shelf Life Testing

FDA guidance - Shelf Life of Medical Devices April 1991

FDA guidance documents on various devices (see references at the end)

Shelf Life or Stability Testing

Shelf life testing is conducted to support the proposed expiration date through

- evaluation of the package integrity for maintaining device sterility (for devices provided sterile by manufacturers) - **packaging shelf life or stability testing (Mr. Steven Turtil's presentation)**

  and

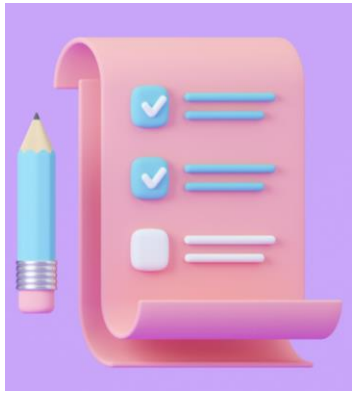
- **evaluation of any changes to device performance or functionality – product shelf life or stability testing (topic for this presentation)**

- The expiration date in the labeling should be in accordance with both test results if applicable, i.e., **minimum value of these two results***

test results	labeled shelf life
If package shelf life > product shelf life	product shelf life
If package shelf life < product shelf life	package shelf life; *unexpired sterile packaged device may be re-packaged and re-sterilized with a reworking procedure, if a validated method has been provided.

Considerations for Establishing Product Shelf Life

- **Define** a set of specifications or criteria for the final device's critical characteristics and performance with tolerance based on the intended use.
- **Identify** raw materials, components, packaging, and process factors; determine if materials and components have their individual shelf life characteristics in addition to their effect on final device shelf life.
- **Develop** an appropriate final device sampling plan (e.g., purpose, number, frequency, criteria and lots) and a sample storage plan (storage and environmental conditions).
- **Develop** a simulation of shipping and handling stresses plan (e.g., vibration) to determine the effect of unusual circumstances.
- **Establish** appropriate accelerated aging parameters when appropriate.
- For absorbable devices, their sensitivity to moisture and temperature should be **addressed** by packaging description (e.g., use of foil) and testing.



General Recommendations for Product Shelf Life Testing

- **Product shelf life testing** should evaluate **all critical characteristics and performance** of aged device samples to ensure they are within the established specifications or criteria. Test report should include test methods, results, and conclusions drawn from the results.
- **Accelerated studies** are acceptable for some products to support tentative dates and storage conditions, as long as they are followed and supported by real time studies. For accelerated aging, we recommend:
  - using the currently FDA-recognized version of **ASTM F1980** and specifying the environmental parameters established to attain the expiration date.
  - specifying the way in which the devices were aged and provide a rationale to explain how the results of shelf life testing are representative of the results if the device were aged in real time.
- **Accelerated studies** may not be appropriate for some products because of their complexity, degradative properties, lack of adequate methodology, or insufficient historical data. In this case, the shelf life should be based on the real-time aged sample test only, e.g., with a short initial shelf life, which will be extended after additional test results.

Designation: F1980 – 21

Standard Guide for
Accelerated Aging of Sterile Barrier Systems and Medical Devices[1]

General Regulatory Requirements for Shelf Life

510(k) – Premarket Notification

- The shelf life of the device should correspond to the duration of aging completed; **a summary** of test reports should be submitted prior to 510(k) clearance.
- Changes in device expiration date do not require a new 510(k). However, where methods or protocols not described in the original 510(k) are used to support new package integrity or shelf life claims, **a new 510(k) may be necessary.**
- For certain devices or components, testing should be conducted on real-time aged samples to confirm the results of the accelerated aging study. This testing should be conducted in parallel with 510(k) review and clearance, with results **documented to file** in the design history file.

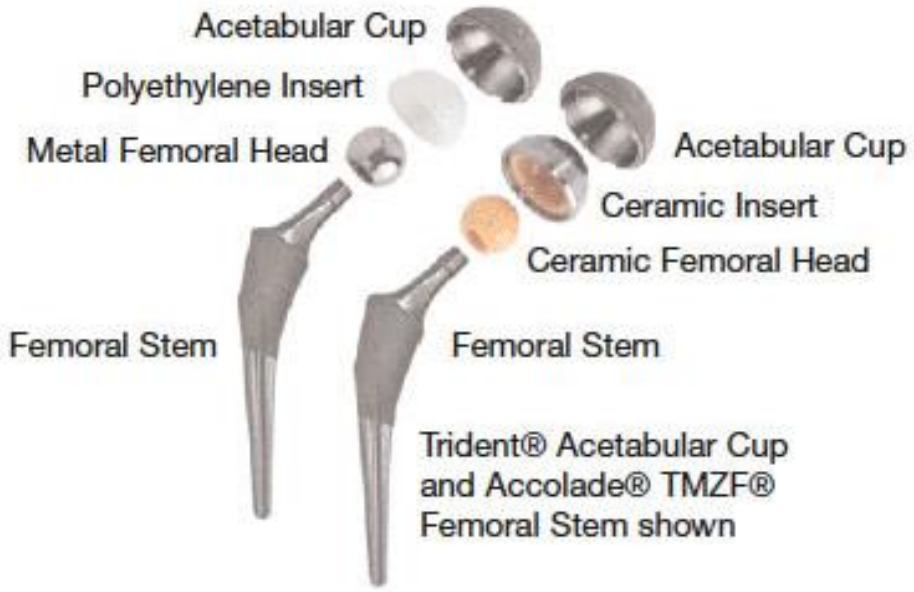
PMA – Premarket Approval

- The approval order shall include the shelf life of the device; **test reports** should be submitted prior to FDA approval.
- If FDA has previously reviewed and accepted a protocol for changes to the expiration date and testing was performed in accordance with that protocol, the change to the expiration date can be made and reported in an annual report. If not, a PMA **supplement** should be submitted for FDA approval (https://www.fda.gov/medical-devices/premarket-approval-pma/pma-frequently-asked-questions#9).

Product Shelf Life Testing – Examples

FDA guidance documents on various devices

Example 1. Joint Arthroplasty Devices



https://www.orthopaedicandsportsclinic.com/about/education.stryker_brochures.english.total_hip.5.php

components	materials	product shelf life testing
acetabular cup	metals (e.g., titanium alloy)	Not needed
femoral stem	Surface coating (e.g., titanium, calcium phosphate)	Yes for coatings in blue
femoral head	metals (e.g., cobalt chrome alloy) or ceramics (e.g., alumina, zirconia)	Yes for materials in blue
acetabular liner	polyethene or ceramics (e.g., alumina, zirconia)	Yes for materials in blue

Example 1a. Polyethylene Implants - Guidance

Characterization of Ultrahigh Molecular Weight Polyethylene (UHMWPE) Used in Orthopedic Devices Guidance, issued on April 26, 2019 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/characterization-ultrahigh-molecular-weight-polyethylene-uhmwpe-used-orthopedic-devices)

- The **mechanical properties** of UHMWPE that contains unstable free radicals may degrade if the product is exposed to air during shelf storage. In addition, the shelf life of UHMWPE that has been irradiated and packaged in an inert environment may be limited by the integrity of the packaging material. Therefore, FDA recommends that the stability of UHMWPE materials used in implantable devices be assessed for the duration of their specified shelf life.
- With respect to evaluating the effects of aging on device performance or functionality, shelf life studies should evaluate the **critical device properties…** (Note: materials and mechanical testing) and repeat all tests that evaluate design components or characteristics that are potentially affected by aging.
- We recommend devices undergo real-time aging to determine definitively the effects of aging on the maintenance of sterility and device performance. If you use devices subjected to accelerated aging, we recommend that you specify the way in which the device was aged and develop a rationale to explain how the results of shelf life testing based on accelerated aging are representative of the results if the device were aged in real time…

https://www.zimmerbiomet.com/en/products-and-solutions/specialties/hip/longevity-high-cross-linked-polyethylene.html

https://www.zimmerbiomet.com/en/products-and-solutions/specialties/hip/vivacit-e-vitamin-e-highly-crosslinked-polyethylene.html

Example 1a. Polyethylene Implants – a recall case

Nonconformance in the integrity of packaging significantly affects the device performance

- The FDA recently issued a **safety communication** on Risks with Exactech Joint Replacement Devices with Defective Packaging to remind patients and health care providers about the joint replacement devices manufactured by Exactech and their recalls in 2021 and 2022. (https://www.fda.gov/medical-devices/safety-communications/risks-exactech-joint-replacement-devices-defective-packaging-fda-safety-communication).
- All Exactech joint replacement devices contain a plastic (polyethylene) component which should be in packaging that contains multiple oxygen barrier layers as indicated in the package specification.
- The recalled devices (including knees, ankles, and hips) were packaged **in defective bags that were missing one of the oxygen barrier layers that protect devices from oxidation, a chemical reaction with oxygen that can degrade plastics over time**. Oxidation can lead to accelerated device wear/failure, and component cracking or fracture, all leading to corrective revision surgery and even bone loss.

Example 1b. Surface Coatings

Recommendations based on current review practices

- With respect to evaluating the effects of aging on performance or functionality of a calcium phosphate coated device, shelf life studies should evaluate the **critical physical, chemical and mechanical properties** of the calcium phosphate coating to ensure the coated device will perform adequately and consistently during the entire proposed shelf life. We recommend that you repeat all tests that evaluate critical coating characteristics that are potentially affected by aging using aged devices.
- We recommend that you provide the protocol(s) used for your shelf life testing, results, and the conclusions drawn from your results. For some **resorbable calcium phosphate coatings**, you should conduct testing on real-time aged samples to confirm the results of the accelerated aging study. This testing should be conducted in parallel with submission review, with results documented to file in the design history file.

www.depuysynthes.com

www.stryker.com

Example 2. Resorbable Bone Void Filler Devices

Recommendations based on current review practices

- Shelf life studies should evaluate the **critical chemical, physical and mechanical properties** of the device that are required to ensure it will perform adequately and consistently.
- Data supporting the expiration date for the final, finished, sterilized, resorbable bone void filler device should be submitted based on **real- time stability testing**. The following parameters should be evaluated upon real time storage over the shelf-life of the product and collected from **at least three production lots**:
    a. Final device chemical characterization (e.g., XRD, FTIR)
    b. Endotoxin level
    c. pH
    d. Water/moisture content
    e. Handling (e.g., ability to absorb hydration fluids, mixing time, setting time, and hardening times, intact, viscosity
    f. Molecular weight distribution for resorbable bone void filler devices with a polymer component
    g. SDS-PAGE and/or differential scanning calorimetry (DSC) to assess the stability (e.g., degradation, physical size assessment, molecular weight, etc.) of resorbable bone void filler devices that contain biologically-derived polymers
    h. Any other parameters identified as part of the device release specification (e.g., appearance, color, dimensions, etc.)
- Because accelerated stability conditions can detrimentally alter the characteristics of resorbable bone void filler devices containing biologically-derived components (e.g., collagen, alginate, gelatin), it is necessary to validate any accelerated stability test with real -time stability testing for the same stability parameters. Once validated, the accelerated stability tests may be used for future stability assessments.

https://www.techsciresearch.com/blog/top-industry-players-in-the-bone-void-fillers-market/1308.html

https://www.zimvie.com/en/spine/biologic-solutions/copios-bone-void.html

Example 3: Patient-Matched Guides and Implants

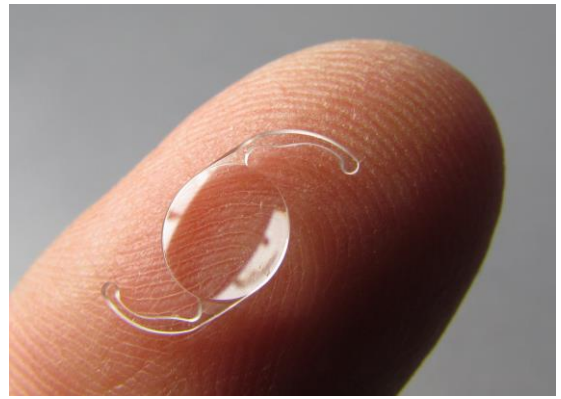
Recommendations based on current review practices

- For patient-matched guides and implants, shelf life should reflect an appropriate duration between the acquisition of patient imaging and the planned surgical intervention to ensure that the anatomical situation has not changed such that guide performance can be affected.
  - Consideration should be taken for the age and growth rate of the patients.
- The shelf life should be based upon the indicated patient pathology and sensitivity of the patient-matched regions to continued disease progression.
- As patient-matched guides rely upon a specific geometrical configuration to establish a unique alignment onto the patient's anatomy, we also recommend that guide deformation as a result of shipping be considered. Additional dimensional testing should demonstrate that guides do not deform following simulated distribution testing.

https://fit2patient.com/clinical-cases/patient-specific-surgical-guides-for-femoral-osteotomy

Other Devices

- **Product shelf life testing** is **device-specific**; please check with the OHT office that regulates the specific device for relevant guidance documents or standards:
  - e.g., ISO 11979-6:2014(E) Ophthalmic implants — Intraocular lenses — Part 6: Shelf-life and transport stability testing
- For more specific questions, please submit a **Pre-Submission** to request feedback per the FDA Guidance entitled "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program)



https://en.wikipedia.org/wiki/Intraocular_lens

References

- Shelf Life of Medical Devices https://www.fda.gov/regulatory-information/search-fda-guidance-documents/shelf-life-medical-devices
- Bone Anchors - Premarket Notification (510(k)) Submissions https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bone-anchors-premarket-notification-510k-submissions
- Characterization of Ultrahigh Molecular Weight Polyethylene (UHMWPE) Used in Orthopedic Devices https://www.fda.gov/regulatory-information/search-fda-guidance-documents/characterization-ultrahigh-molecular-weight-polyethylene-uhmwpe-used-orthopedic-devices
- Deciding When to Submit a 510(k) for a Change to an Existing Device https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device
- Recognized consensus standards database https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm
- FDA Guidance Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program
- PMA Frequently Asked Questions | FDA: https://www.fda.gov/medical-devices/premarket-approval-pma/pma-frequently-asked-questions#9
- ANSI/AAMI/ISO 14971: 2019 Medical devices—Application of risk management to medical devices
- ASTM F1980-21 Standard Guide for Accelerated Aging of Sterile Barrier Systems and Medical Devices
- ISO 11979-6:2014(E) Ophthalmic implants — Intraocular lenses — Part 6: Shelf-life and transport stability testing

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Thank You!

QUESTIONS?

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