Successful Practices for Navigating Post-Market Changes

Industry Experience on behalf of Combination Products Coalition

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Disclaimer

The views expressed herein represent those of the author and do not necessarily represent the views or practices of the author's employer or any other party.

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Agenda

- Combination Product Change Management Landscape
- Change Control Process
- Determining Reporting Category

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Combination Product Change Management Landscape

Drug/Biologic PMOA Combination Products

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Change Control for Combination Products

- 21 CFR 4 cGMP for Combination Products incorporates 21 CFR 820.30(i) Design Changes
  - *establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation*

- Changes to approved applications (BLAs and NDAs) are regulated by:
  - 21 CFR 314.70 (NDA)
  - 21 CFR 601.12 (BLA)

- A change to a product, production process, quality controls, equipment, or facilities is required to be reported to FDA in:
  - A supplement requiring approval prior to distribution (substantial risk)
  - A supplement at least 30 days prior to distribution (moderate risk)
  - In an annual report (minimal risk)

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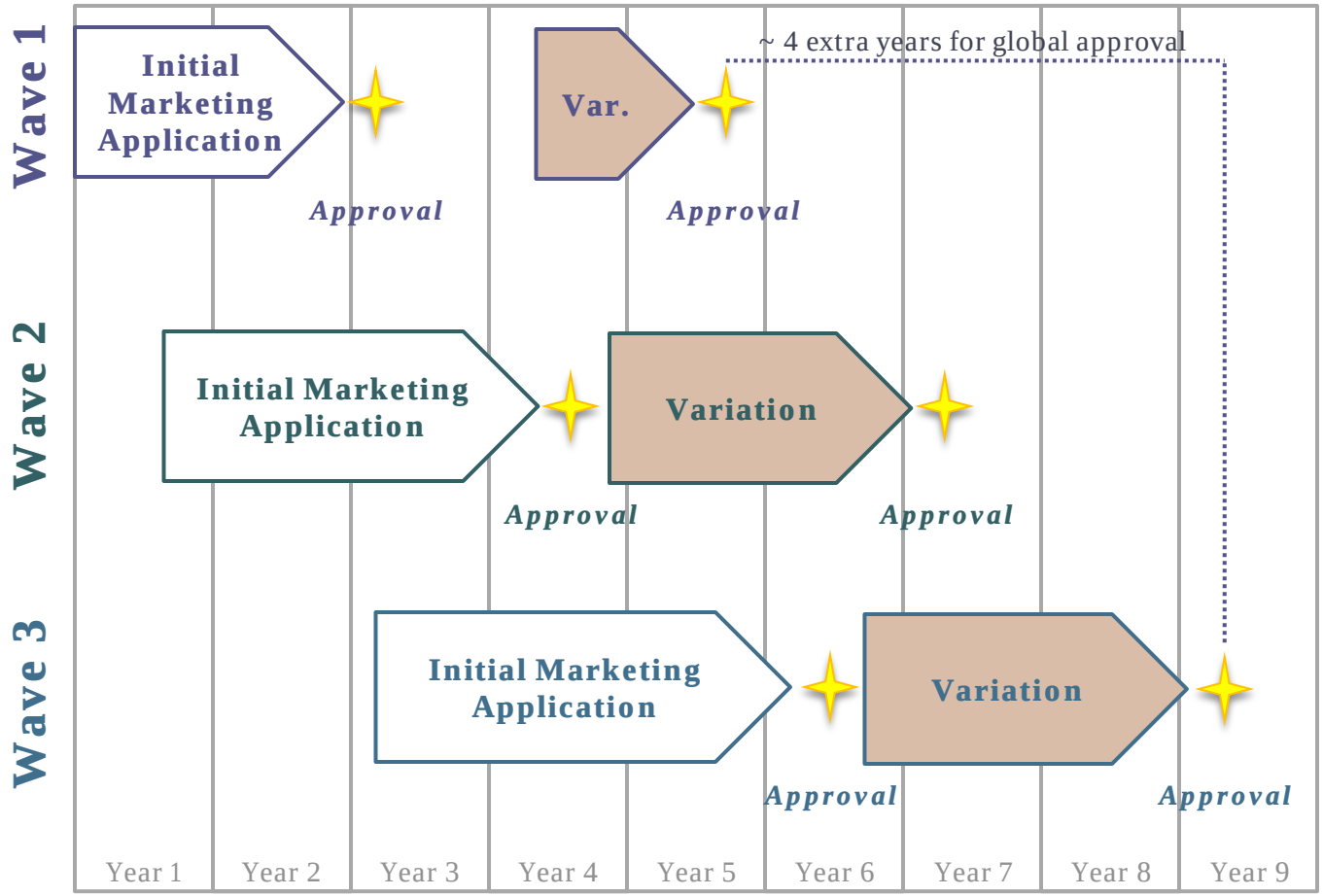
Realities of Change Management…



Global implementation timeline impacted to a greater extent due to ongoing initial reviews

Aim to minimize commitments in Wave 2/3 markets to shorten overall implementation timelines

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Begin with the End in Mind

Change Management *STARTS* with the Initial Submission

- Build submission/submission structure to enable streamlined post-approval changes
- Understand what areas are likely to change most frequently
- Avoid repeating same information multiple times (especially when it would be subject to post approval change), use hyperlinks
- Take care with the level of detail provided in commitment sections
  - Find the right balance to provide necessary information to meet requirements but not too much detail that could increase change burden
- Deliberate understanding/declaration of established conditions

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Purchasing Controls

Critical for managing changes throughout the lifecycle

- Successful implementation of purchasing controls can make for proactive rather than reactive regulatory strategy
- Vital for combination products, as most include purchased materials/components/device assemblies
- Design only as good as purchasing controls
  - without strong purchasing controls, design can change ***without you even knowing***
- Supply agreements:
  - Customers and suppliers should agree on notification and approval of changes and include these terms in agreements
  - Suppliers should ensure that THEIR suppliers have adequate change control programs in place

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Change Control Process

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Change Control Process

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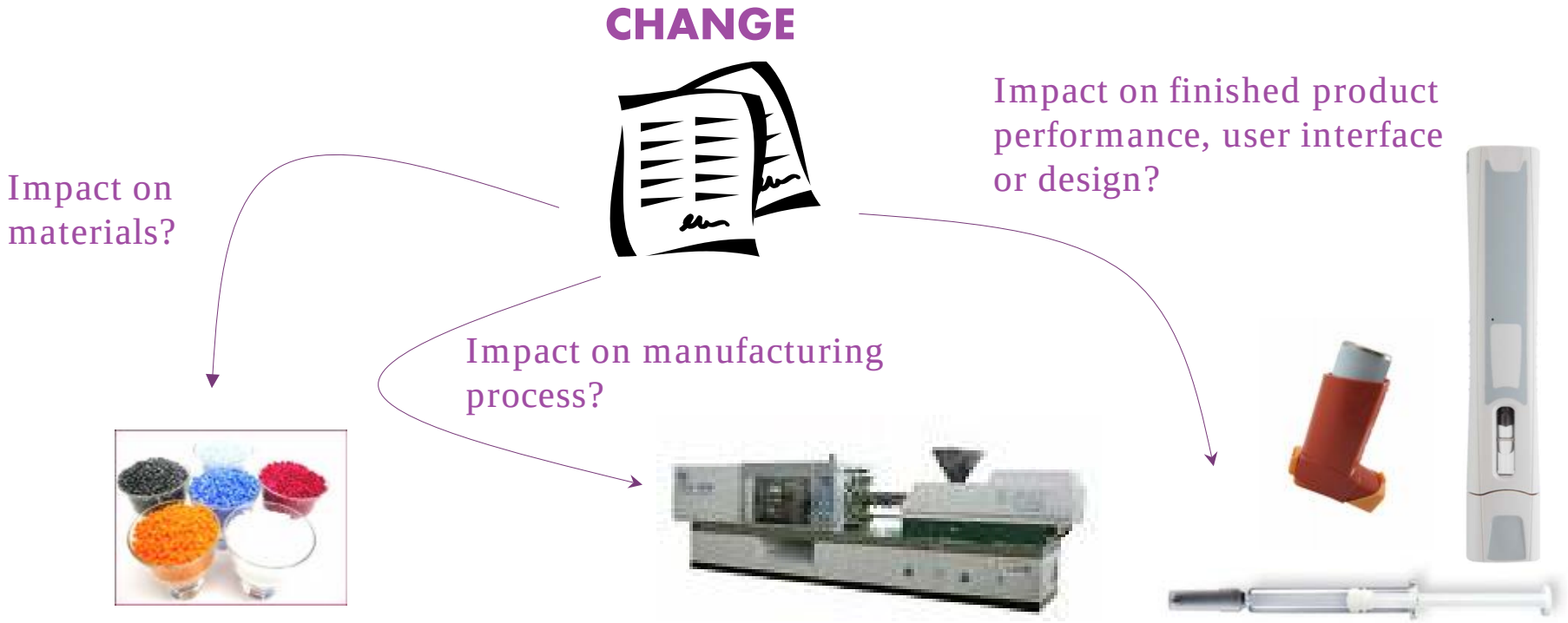
Understanding & Evaluation of Changes

Pre-cursor to Regulatory Assessment



- Determine impact on product quality, safety & efficacy, usability, and process validation
- Understand the current/proposed future state – including any differences in function or user experience, overall risk profile
- ISO 20069 (under development) will provide a framework for assessing changes

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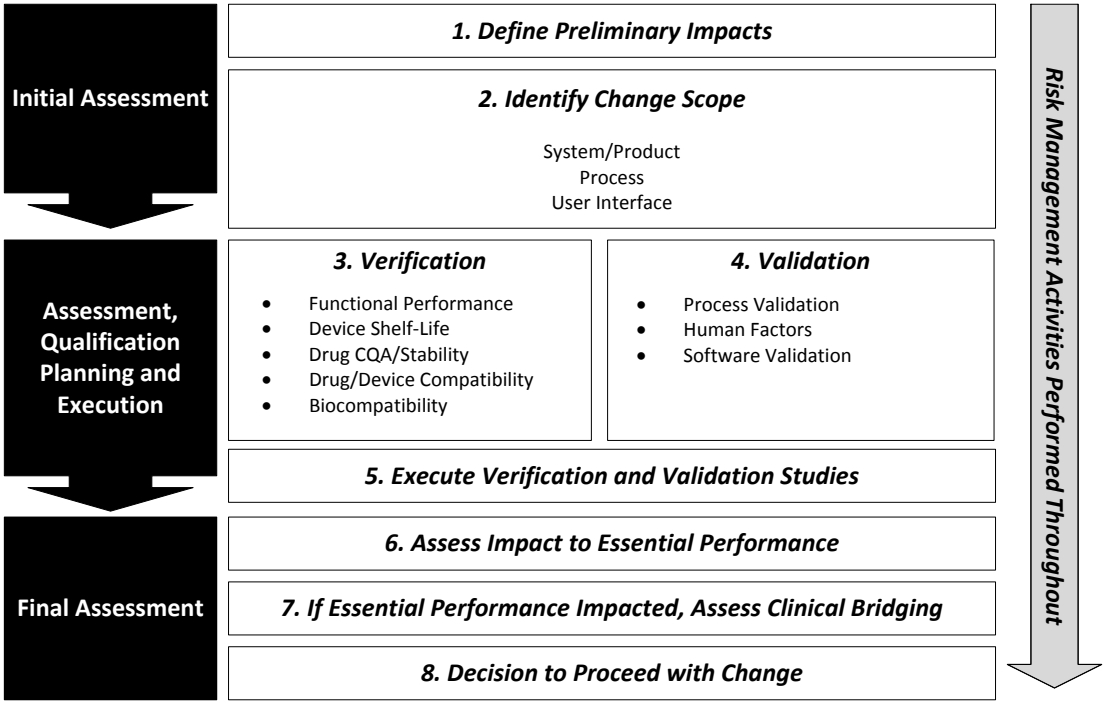
ISO 20069: Device change management of combination products for administration of medicinal products

(under development, ISO/TC 84 WG15)

- Intended as a guidance for manufacturers to manage changes made to combination products intended to deliver a specific pharmaceutical product
- Current Approach:
  - Linked to risk management & assessment of impacts to essential performance
  - Process flow central to standard with analysis approaches presented
- Standard not intended to address regulatory reporting requirements (defers to national legislation)



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Determining Reporting Category

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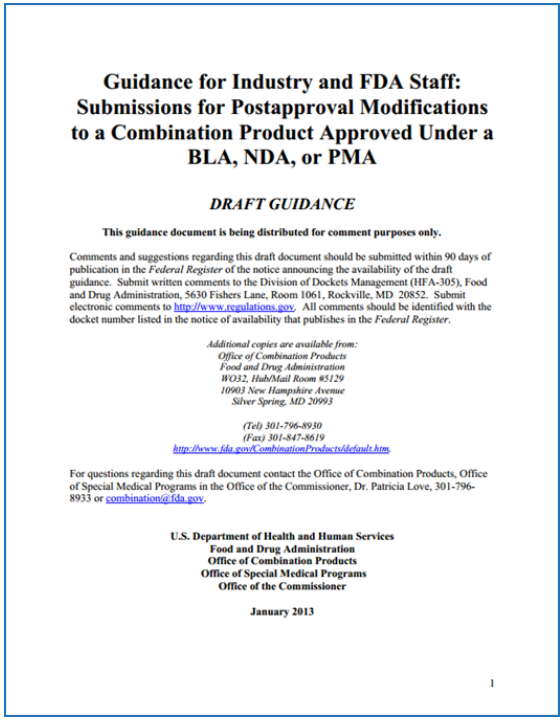
Approach to Determining Reporting Category for Device Constituent Related Changes

- Combination Products draft guidance (2013) based upon existing FDA post approval guidance documents:
  - Changes to an Approved NDA or ANDA
  - Changes to an Approved Application – Biological Products
  - Modifications to Devices Subject to Premarket Approval (PMA)
  - 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day HDE Supplements for Manufacturing Method or Process Changes
  - ➢ *Submission type for constituent change based upon original combo product application pathway + most comparable post approval application type*



Guidance for Industry and FDA Staff: Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies are available from:
Office of Combination Products
Food and Drug Administration
WO32, Hub/Mail Room #5129
10903 New Hampshire Avenue
Silver Spring, MD 20993

(Tel) 301-796-8930
(Fax) 301-847-8619
http://www.fda.gov/CombinationProducts/default.htm

For questions regarding this draft document contact the Office of Combination Products, Office of Special Medical Programs in the Office of the Commissioner, Dr. Patricia Love, 301-796-8933 or combination@fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products
Office of Special Medical Programs
Office of the Commissioner

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- The following guidances are also consulted by industry:
  - CMC Post Approval Manufacturing Changes to be Documented in Annual Reports
  - PMA Annual Reportable Changes Guidance
  - 510(k) Guidance

Logical approach, but not easy to implement for minor/moderate changes

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Challenges with Identifying Appropriate Pathway for Device Constituent Changes

Could you identify the appropriate pathway for a change to the spring component of an autoinjector?

Table 1: Type of NDA/BLA Submission for a Change in a Device Constituent Part of a Combination Product Approved under an NDA/BLA

If the Device Constituent Part Were a Stand-Alone Device Approved under a PMA and the Change Would Have Required the Following Submission		Then Submit Information on the Device Change Using This Type of NDA/BLA* Submission for the Combination Product
PMA Original		**NDA/BLA Original**
PMA Panel-Track Supplement (New indication/population, without any other change to the constituent parts, supported by new clinical data and the original preclinical data)		**Prior Approval Supplement (Efficacy)**
PMA 180-day Supplement • Design • Manufacturing site change • Labeling change including nomenclature (And with a change from the next column)	Design change and labeling change supported by new preclinical and/or limited confirmatory clinical data	**Prior Approval Supplement (Efficacy)**
	Changes supported by limited confirmatory data (i.e., clinical bioequivalence or bioavailability data)	**Prior Approval Supplement (Manufacturing)** (With or without labeling changes)
	Manufacturing site change not requiring any clinical data	
	Significant labeling change that does not qualify for a Special PMA Supplement - Changes Being Effected, does not change the indication, and does not include a design change	**Prior Approval Supplement (Labeling)**
PMA Real-Time Supplement (Design or labeling change that does not require clinical data and for which the data provided fall within only one scientific discipline, e.g., electrical engineering, microbiology, or sterilization)		**Prior Approval Supplement (Manufacturing or Labeling)**
30-day Notice (Manufacturing process or method change only)		**30-day Changes Being Effected**
Special PMA Supplement - Changes Being Effected		**Changes Being Effected**
PMA Periodic Report		**Annual Report**

***Time lines and FDA-industry interactive procedures will be those of the NDA/BLA**

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Determining Reporting Category

CPC Position

- Reporting Category should be based on a combination of potential for direct adverse effects (substantial, moderate, minimal) on device **Essential Performance (EP) or drug (CQA)** and changes which affect **Established Conditions (EC)**
  - **Essential Performance (EP) -** intended function that is necessary to achieve freedom from unacceptable harm; and/or for acceptable delivery of the dose
  - **Established Conditions (EC)** – certain binding information or elements concerning the manufacture and control of a pharmaceutical product found in a submission that assure process performance and desired quality of an approved/licensed product. Includes:
    - description of the product
    - elements of the manufacturing process
    - facilities and certain equipment
    - specifications [i.e., test, method and criteria]
    - other elements of the associated control strategy (e.g. storage conditions or shelf-life)
- CPC recently submitted guiding principles and specific examples to FDA for consideration in relation to the guidance on post-approval changes to combination products

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Not all changes are created equal

CPC Recommends Flexible Guidance

- Determining reporting category is a fact-dependent analysis
- The SAME change may have different reporting depending on the circumstances
- For example – an autoinjector spring change could be reported as a PAS, Annual Report or not reported

Reporting Category:	PAS	Annual Report	Not Reported
Example:	• Spring force change	• Spring force change	• Steel galvanization process change
Circumstances of change:	• Change results in change to product release specification, e.g., delivery time	• Change does not result in any changed to product release specifications	• Properties/info. that does not have an adverse effect on drug or device
Rationale / Justification:	• Change to EC (registered release specification) • Substantial potential impact on device essential performance and drug CQAs	• No EC change (no change to registered controls) • Minimal potential impact on device essential performance and drug CQAs	• No EC change (detail not included in filing) • Minimal potential impact on device essential performance and drug CQAs

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Summary

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Summary

- Change management for combination products relies on strong quality systems
  - Purchasing controls very important!
- Assessment of changes and potential for impact to device EP/drug CQA as qualification plan is developed
- Reporting category ideally derived from impact to device EP/drug CQA and registered Established Conditions

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Thank you!!

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Useful Links

- *Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA* (Draft, Jan 2013) http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM336230.pdf
- *Changes to an Approved NDA or ANDA* (Apr 2004) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm077097.pdf and Q&A (Jan 2001) - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm122871.pdf
- *Changes to an Approved Application: Biological Products* (Jul 1997) - http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM170166.pdf
- *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (Jul 1997) - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm124805.pdf
- *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports* (March 2014) - http://www.fda.gov/downloads/Drugs/.../Guidances/UCM217043.pdf
- *Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process* (Dec 2008) - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089360.pdf
- *30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes* (Apr 2011) - http://www.fda.gov/downloads/MedicalDevices/.../ucm080194.pdf
- *Deciding When to Submit a 510(k) for a Change to an Existing Device* (Draft, Aug 2016) http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm514771.pdf

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Case Study – Part E

1. For each of the proposed changes to increase capacity, what would be the post-approval submission reporting category? Describe the qualification testing that would be needed to qualify each change.
2. Would the reporting categories be affected if these capacity-related changes were introduced at the same time or sequenced.
3. Describe the post-approval submission reporting category for the introduction of BlockUVInject-1. What data would be needed to qualify the change

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Case Study – Part C

1. What post-approval submissions are required for the changes to the BlockUVInjector prefilled injection device?
2. How should BestEver Assess the ability of patients to perform the necessary calculations correctly? What data would need to be included in the submissions to support the revised BlockUV and BlockUVInjector labeling?
3. What post-approval submissions are required for the addition of the Bluetooth and Wi-Fi connectivity?

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