TEAM-NB WG Article 117

TEAM-NB Perspective on Life Cycle Management under Article 117 / MDR.

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Colm O'Rourke - NSAI

EMA Workshop 27 November 2020

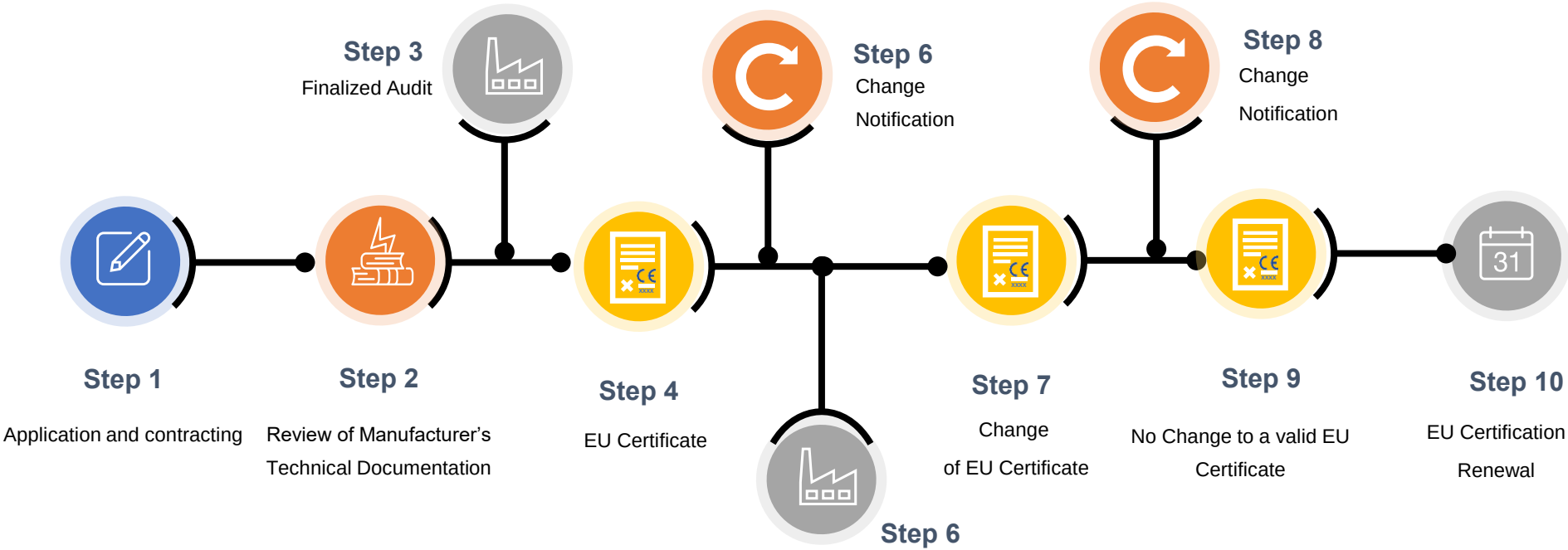
Agenda

1. Purpose of todays presentation
2. Current NB practices: Certification and device changes
3. Existing guidance on device changes
4. TEAM NB position paper on life cycle management
5. Examples

Purpose of Todays Presentation

- Present the draft Team-NB Position Paper on Life Cycle Management
- Communicate the criteria Team-NB uses to determine substantial changes
- Highlight any discrepancies which may exist between Team-NB's and industries determination of substantial changes
- Seek input from EMA/NCA on how best to resolve any such discrepancies

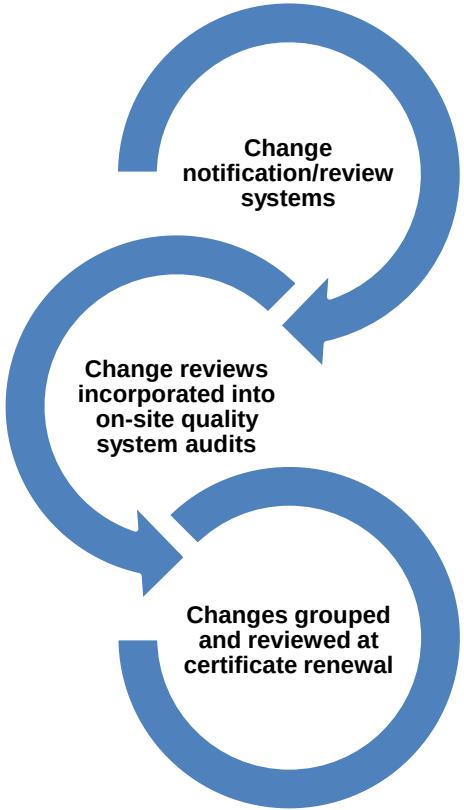
Process of EU Certification for Medical Devices



Current NB practices – device changes

NB's have several ways to handle device changes under MDD/MDR:

- Stratification of changes depending on device classification



Current NB practices – device changes

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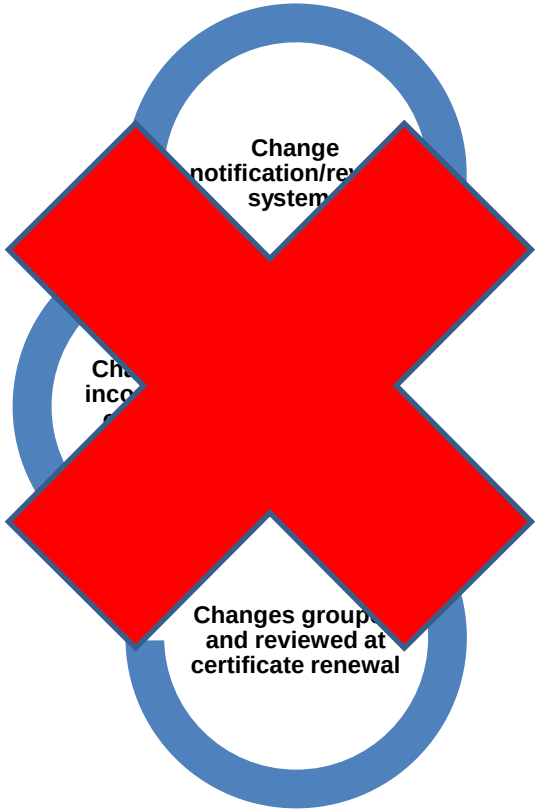
These options are not available at present to NB's or industry under Art. 117 NBOp system

more robust system must be developed going forward – Cooperation with EMA/NCA/NB's/Industry needed



Existing Guidance relevant to assess changes

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

04 March 2020
EMA/CHMP/ICH/804273/2017
Committee for Medicinal Products for Human Use

ICH guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management

Step 5

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

21 October 2019 Rev.1
EMA/37991/2019
Human Medicines Evaluation Division

Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)

EUROPEAN MEDICINES A
SCIENCE MEDICINES

8 April 2020
EMA/CHMP/QWP/BWP/259165/2019
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the quality requirements for drug-device combinations

INTERNATIONAL STANDARD

ISO 20069

First edition
2019-08

Guidance for assessment and evaluation of changes to drug delivery systems

Gestion des changements d'appareils dans les combinaisons de produits pour l'administration de médicaments

EUROPEAN COMMISSION

Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures

(2013/C 223/01)

NBOG's Best Practice Guide

applicable for ☒ AIMDD, ☒ MDD, and ☒ IVDD

2014-3

Guidance for manufacturers and Notified Bodies on reporting of Design Changes and Changes of the Quality System

Scope	Group Deliverables	Consult prior to MDCG**	Planned MDCG Endorsement	Additional Comments
** Stakeholders are observers in 13 MDCG subgroups and are consulted on a regular basis; further to that other MDCG subgroups are consulted as indicated				
1. Notified Bodies Oversight (NBO)[1]				
	(i) Article 120(3)			
MDR	*Guidance on NB opinions on the conformity of the device part according to Article 117 MDR*			B&C

Existing Guidance relevant to assess changes

EMA Q&A 21 October 2019 Rev.1 EMA/37991/2019

In cases where the MAH introduces substantial changes to the medical device component, a new (updated) EU certificate / declaration of conformity / opinion from a notified body will need to be provided as part of the variation/extension application, as appropriate.

Changes to the device component are considered substantial if the changes affect the performance and safety characteristics of the device.

It is the responsibility of the marketing authorisation holder to determine if the changes are substantial and EMA/NCAs expect that the MAHs liaise with the notified body and submit to EMA/NCA the necessary documentation as part of a variation/extension application.

This requirement applies to all marketing authorisations, even those that had complied with Article 117 MDR with their initial MAA.

If the variation does not affect the medical device then a new/updated notified body opinion/ certificate is not required.

- In case of substantial changes to device, (re)assessment by NB and NBOp required as part of variation submission
- Applies to all marketing authorisations as of 26 May 2021

Existing Guidance relevant to assess changes

EMA Q&A 21 October 2019 Rev.1 EMA/37991/2019

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If the variation does not affect the medical device then a new/updated notified body opinion/ certificate is not required.

- Responsibility of MAH to determine if changes are substantial
  - **Do** liaise with NB to obtain NBOp
  - NB **can not** determine if change is substantial – unable to provide advice

- Current variation guidance is unclear on changes to the device part
  Not clear on how to determine whether changes are substantial

?

Team-NB Position Paper

TEAM NB
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Editor: Françoise SCHLEMMER Date: September 2020

Position paper for the interpretation of changes in relation to a NB Opinion as required under Art. 117 of Medical Device Regulation (EU)2017/745

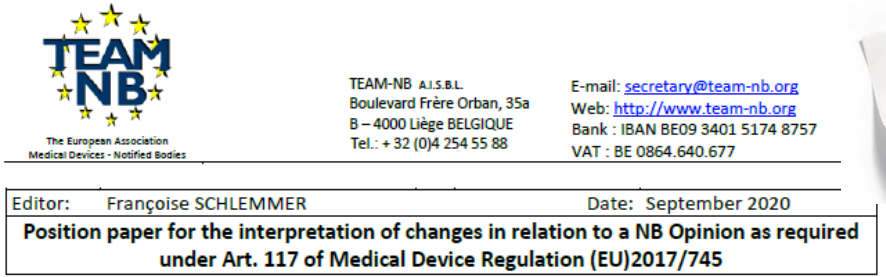
Intended to be a discussion of device related changes which will potentially require a new or revised NBOp

To create alignment between Notified Bodies on interpretation of substantial changes

- **NOT intended to provide any position on submission of a variation and type of variation**

Based on existing NBOG best practice guide, MDCG guidance 2020-3 and ISO 20069

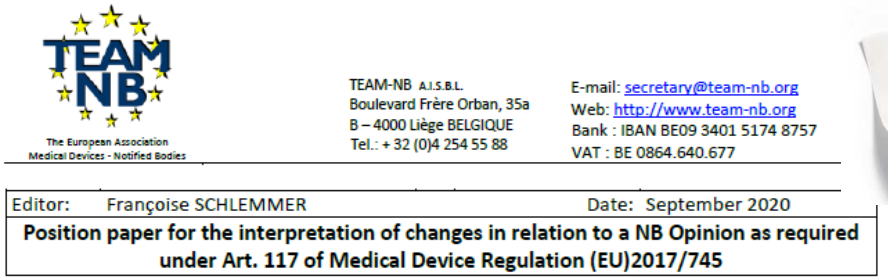
Team-NB Position Paper



Development so far:

- Team-NB received comments from EMA/NCA
- Draft position paper provided to industry participants of todays workshop
- Upon completion and agreement by NB's, the paper will be published as Team-NB position paper

Team-NB Position Paper



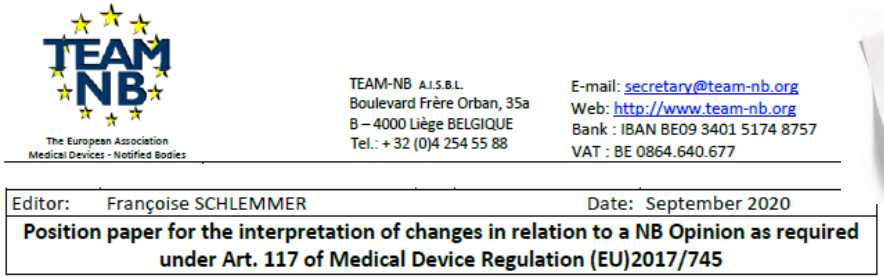
<u>What is included:</u>

- Definition of substantial change

  A change is considered substantial when it is **likely** to have an impact in terms of:

- Device safety or performance
- Compliance with applicable GSPR
- Device related claims and intended use / change in users.

Team-NB Position Paper



<u>What is included:</u>

- Main Chart: Change of an existing device part in a drug-device combination product
- 5 Sub Charts:

1. Substantial changes in the intended purpose
2. Substantial changes in the design or performance specification
3. Substantial changes of a component or a material
4. Substantial changes of sterilization method or packaging with impact to the sterilization
5. Substantial changes in the design - Software Changes

Team-NB Position Paper

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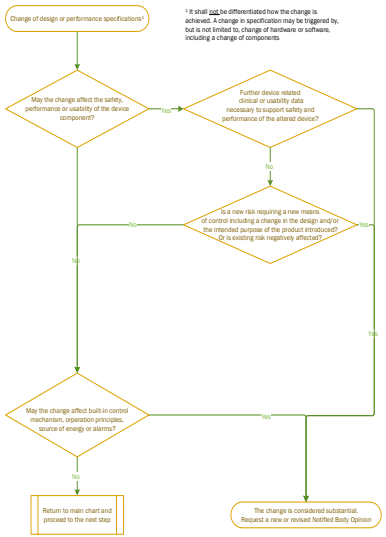
What is included:

- Explanatory notes
- Examples



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Please Note:

- Changes with respect to QMS are **outside** the scope

- Proposed device related changes should be classified (sub/non-sub) at the outset - Subsequent V&V data should not alter the status of the change
  - E.g. Situations where the V&V documentation of a new device component supports compliance to previous device component specifications **does not** always mean the change is non-substantial

Team-NB Position Paper

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The European Association Medical Devices - Notified Bodies

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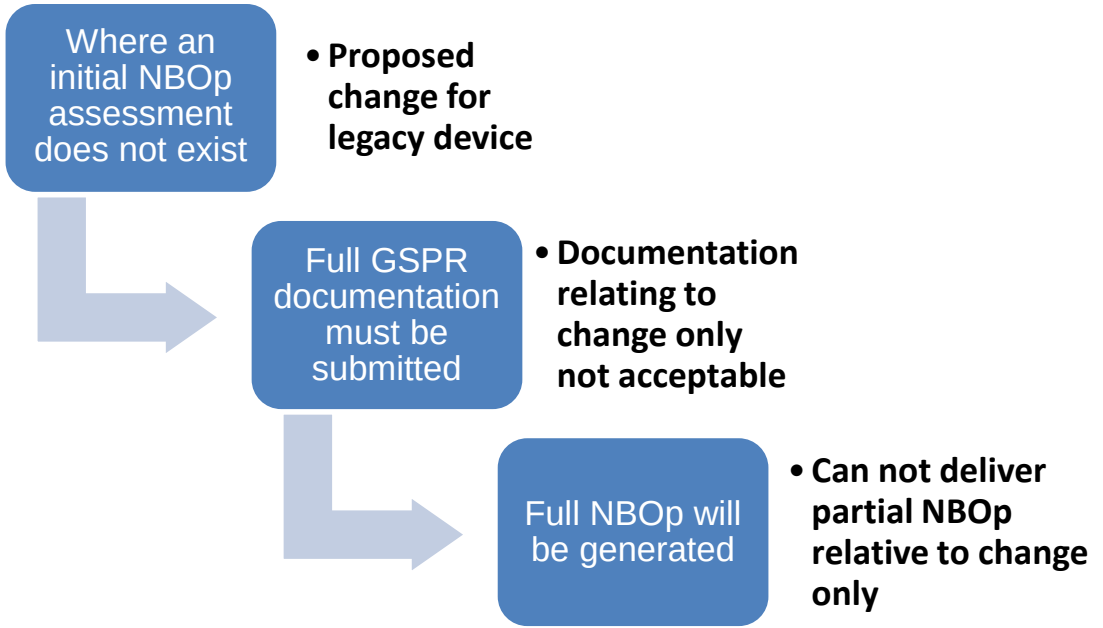
Please Note:

- Changes on legacy devices:



Examples

How to follow flow charts:

- If considering multiple changes, assess each change separately
- Begin with main flow chart always and move through until you reach the diamond which best fits your proposed change
- Move now to the specific flow chart relative to your proposed change
- Work your way through the specific flow chart
- The end result will either be –
  - The chart determines the proposed change is considered substantial
  - Return to main chart and proceed through until you have addressed all diamonds and reached the conclusion that the proposed change is considered non-substantial

Examples

1.

Efpia: Change in formulation (higher drug concentration) results in a solution viscosity change although formulation change has no impact on the clinical efficacy and safety of the medicinal product

- *Subsequent V&V data supports no change in performance from unmodified pen.*

Efpia determination: non-substantial change

Examples

1.

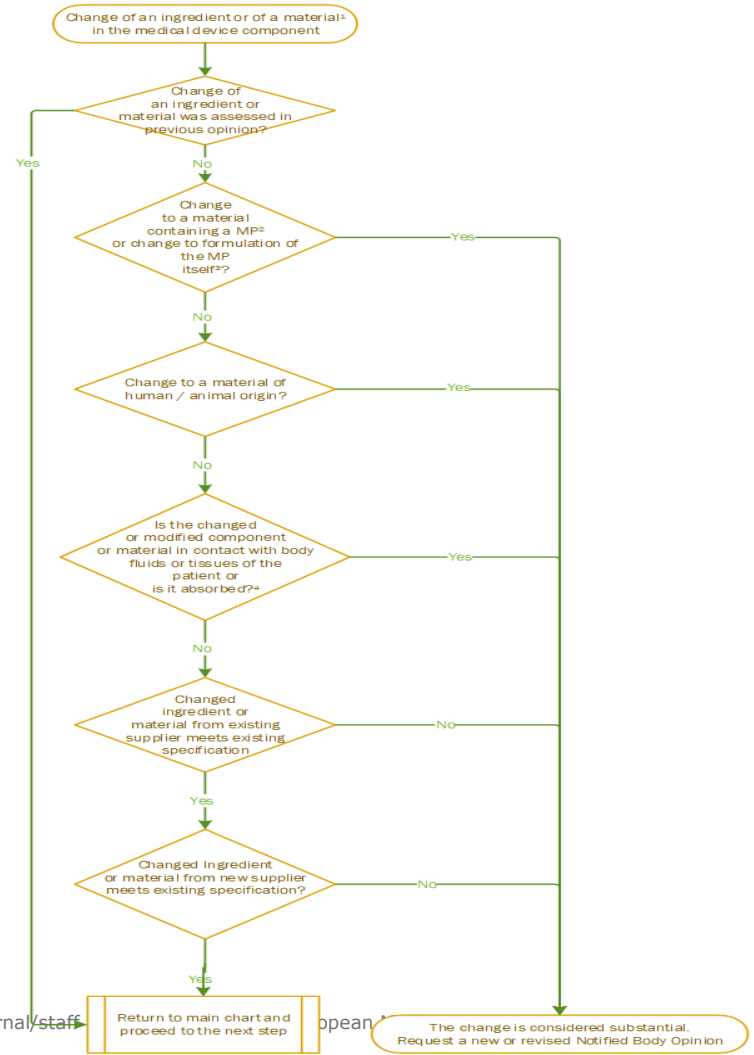
Flowchart n°3:
Substantial changes of a component or a material

[1] These relate to changes involving existing ingredients and materials. New ingredients or materials are considered substantial changes.

[2] MP: Medicinal product

[3] Including a change in its manufacturing process, beyond existing specification. A change in the characteristics oft he drug could impact the performance oft he device part (e.g. change in volume, change in viscosity)

[4] Example:
- Implantable device
- oral ingestible
- external communicating device



Examples

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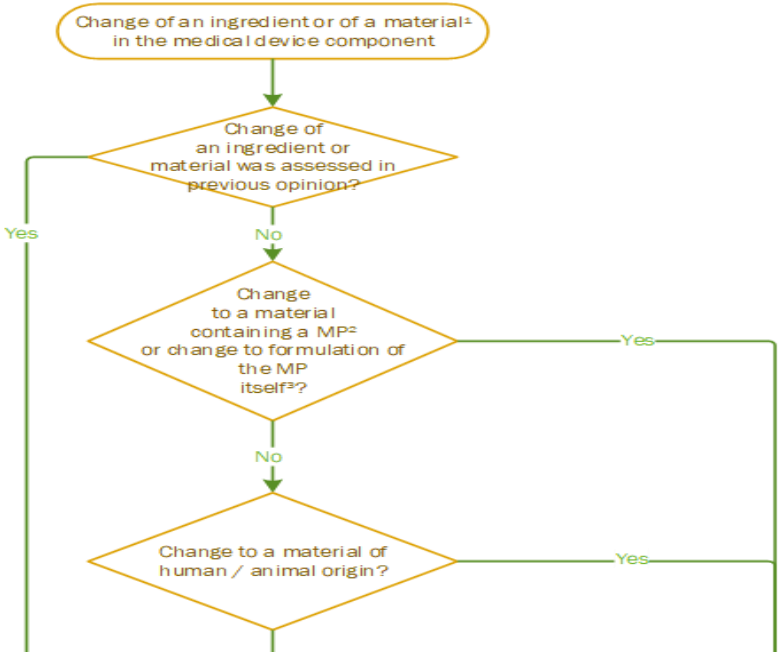

Examples

1. Flowchart n°3: Substantial changes of a component or a material

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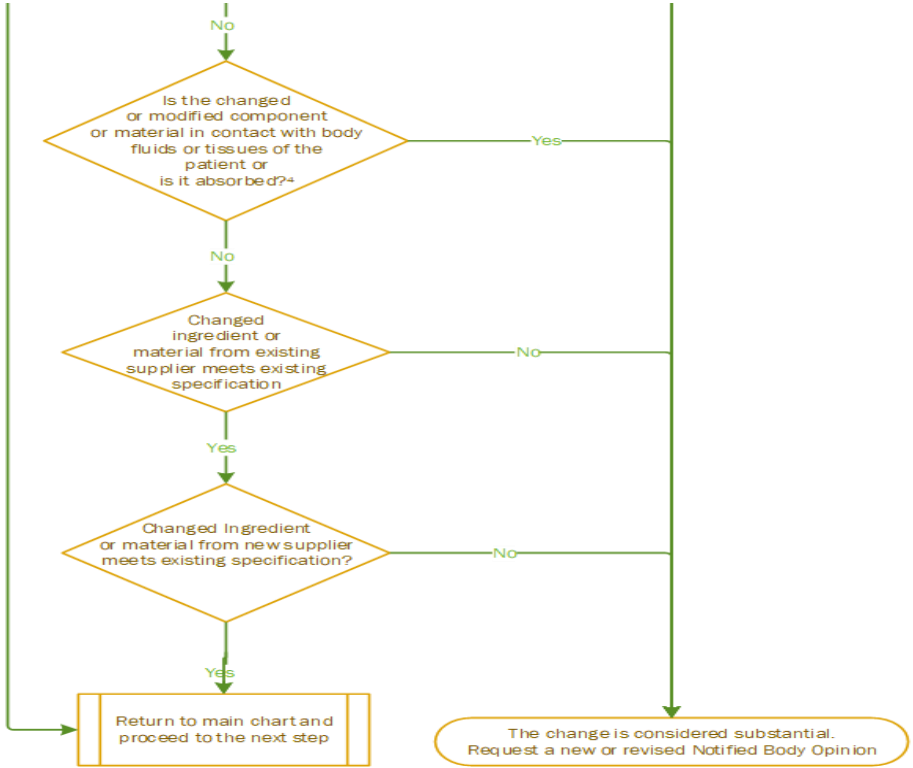

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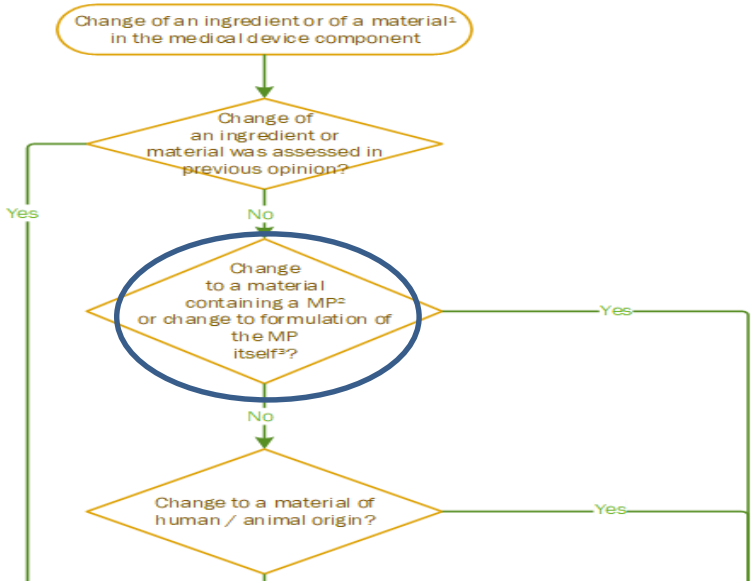


Examples

1.

Note: Second diamond:

- *Change to a material containing an MP or change to the MP itself = Yes*
- *A change in the characteristics of the drug could impact the performance of the device part (e.g. change in viscosity may lead to different injection force, accuracy of dosing).*
- *Then change is considered* substantial

Proposed device related changes should be classified at the outset.

Examples

2.

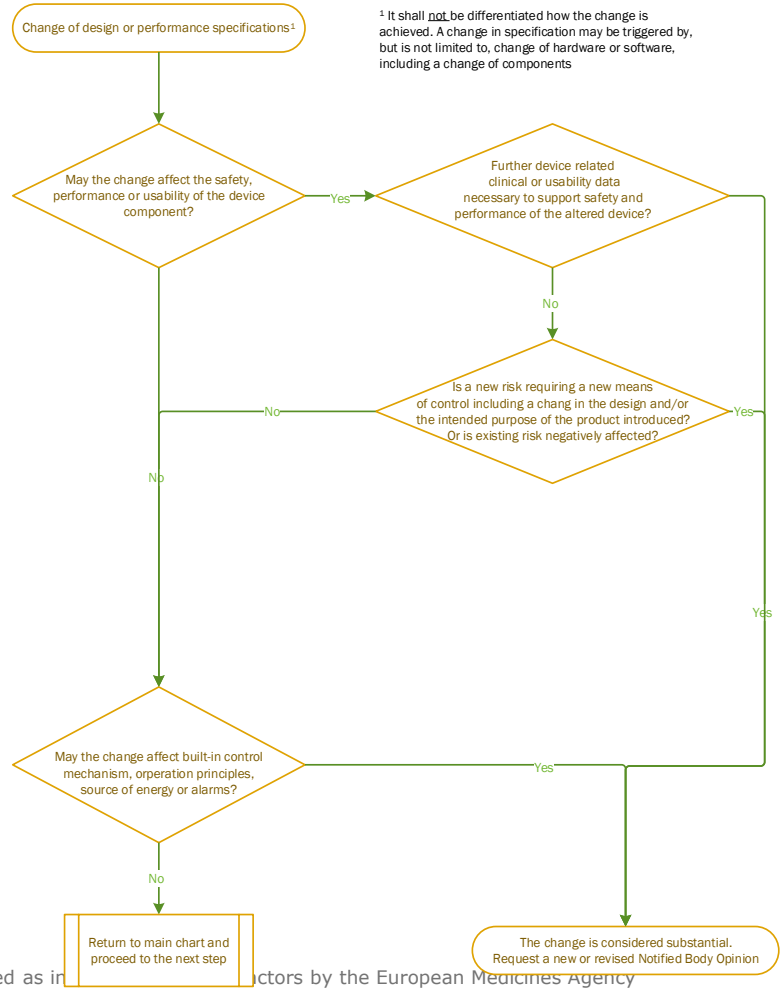
Efpia: Internal needle dimension of staked needle is changed but route of administration remains unchanged (needle length giving SC admin)

Efpia determination: non-substantial change

Examples

2.

Flowchart n°2:
Substantial changes in the design or performance specification



Examples

2.

Flowchart n°2:
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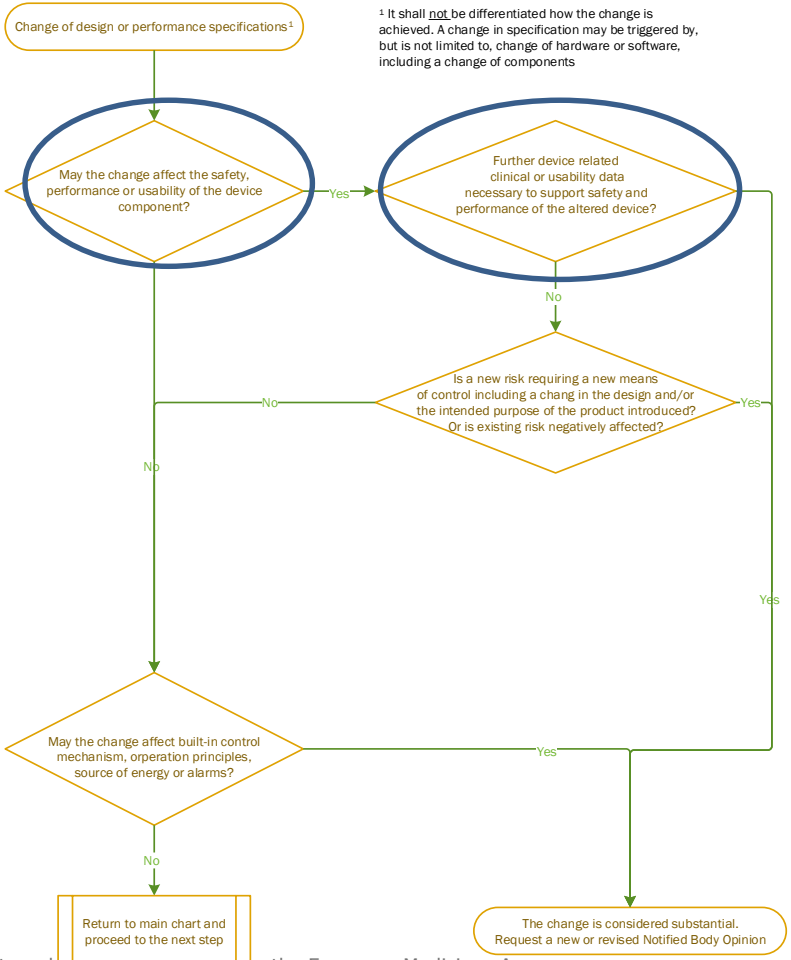

Examples

2.

Note: first diamond/ second diamond:

- *Change in internal dimensions may impact the injection force and thus performance claims, usability or even safety*
  - *Previous experience: NB received Field safety notices after change in dimensions due to change in injection force*

substantial change

Examples

3.

Efpia: CE declaration for **needle safety guard** used with staked prefilled syringe is no longer supported by supplier; deletion of a medical device in MAA

Safety & performance of safety needle component will be managed by manufacturer in overall conformance of staked prefilled syringe against Annex I requirements for single-integral DDC

Examples

3.

Needle safety guard component as medical device will be removed but will remain as part of the DDC and will be managed through assessment of GSPRs Annex I.

Not substantial as no changes in design or specifications. Only administrative change

Caveat:
Q&A EMA:
If DoC or Cert is not available then NBOp must be provided:

Table 1. Summary of changes for **Marketing Authorisations Applications involving integral DDCs**

Type of integral device included in the MAA	New submissions as of 26th May 2020
Class I (sterile, measuring or reusable surgical instrument*), Class IIa, Class IIb Class III	The marketing authorisation dossier should include a **Declaration of Conformity or EU notified body certificate** for the medical device, where available. If the above mentioned documentation is not available then **an opinion** ** **from a notified body** must be provided for the medical device
Class I (non-sterile, non-measuring, or non-reusable surgical instrument)	The marketing authorisation dossier should include a **Declaration of Conformity** for the medical device, where available.
* the reader should note that integral DDC as referred to in second subparagraph of Regulation 2017/745 Article 1(9) are not reusable **opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to Regulation 2017/745	

Conclusion & Challenges

Alignment and cooperation is key

- Different interpretations on substantial changes
- Stakeholders must align on how proposed device changes are classified - proposed device related changes should be classified (sub/non-sub) at the outset
- Current variation guidance is deficient in this regard

What are the next steps?

- If a device change is considered substantial per Team-NB flow paper?

→ NBOp request → variation submission?

- NB's will be available to issue/ revise NBOp's in response to substantial changes

Who will make the final decision on the status of the proposed change?

- Should NB's be involved in the decision-making process?
- If so, is there a regulatory basis for this?

Thank you for your attention!

Additional slides

Examples

4.

Efpia: Change to the valve used in a pMDI for a maintenance therapy product. The material of construction of one of the components of the pMDI has been changed due to discontinuation of the current material by the manufacturer

Efpia determination: non-substantial change

Examples

4.

Flowchart n°3:
Substantial changes of a component or a material

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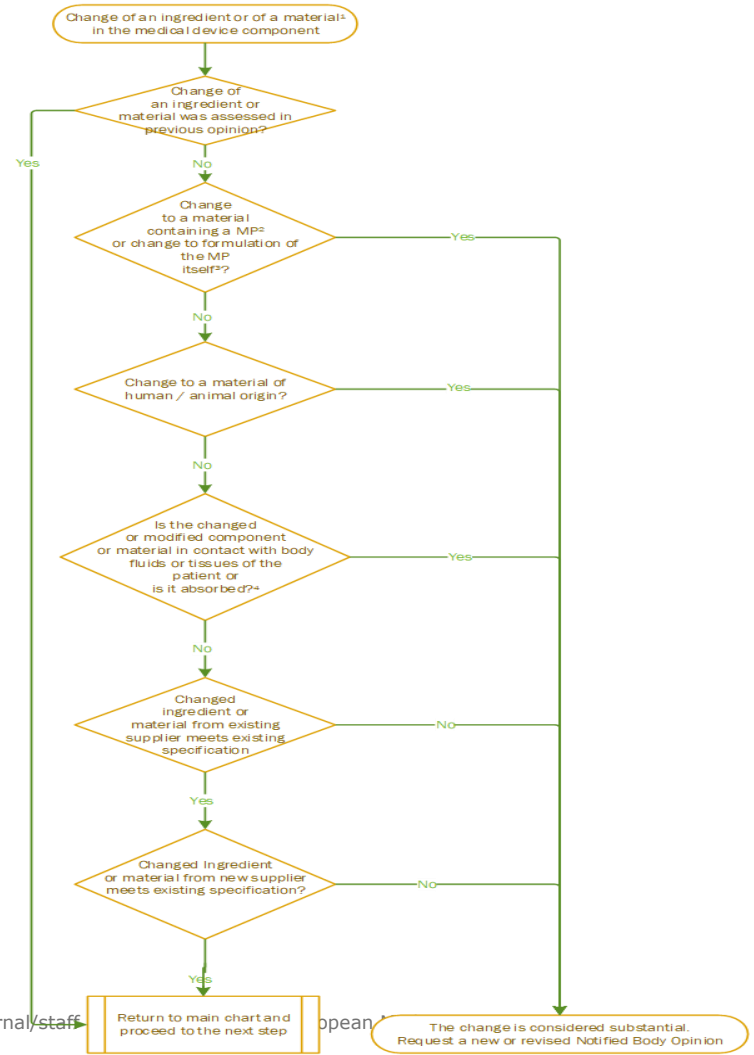

Examples

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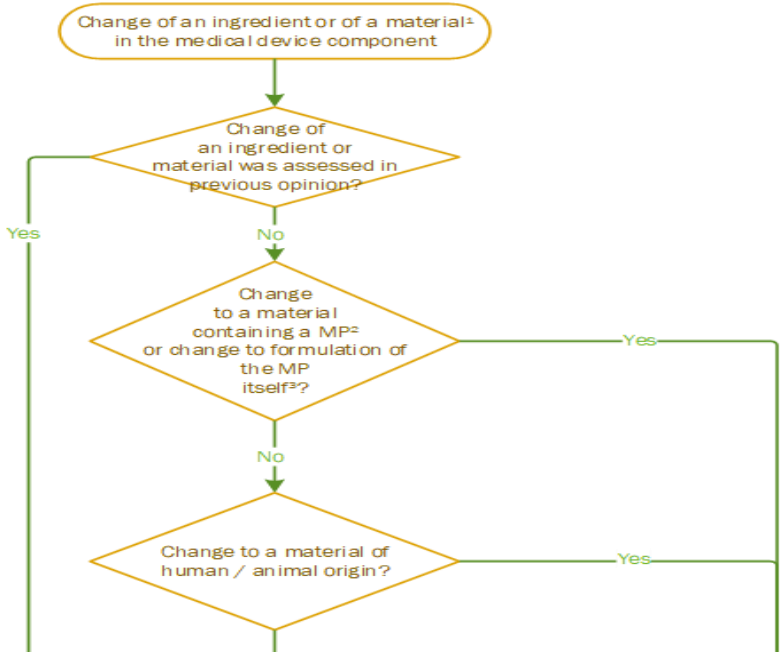

Examples

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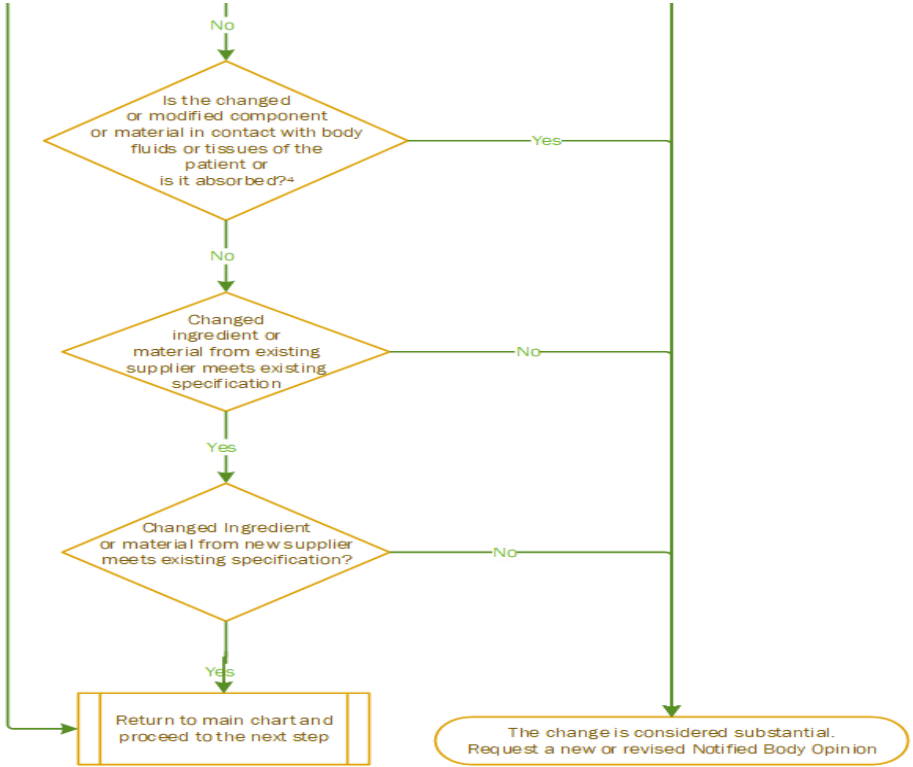

Examples

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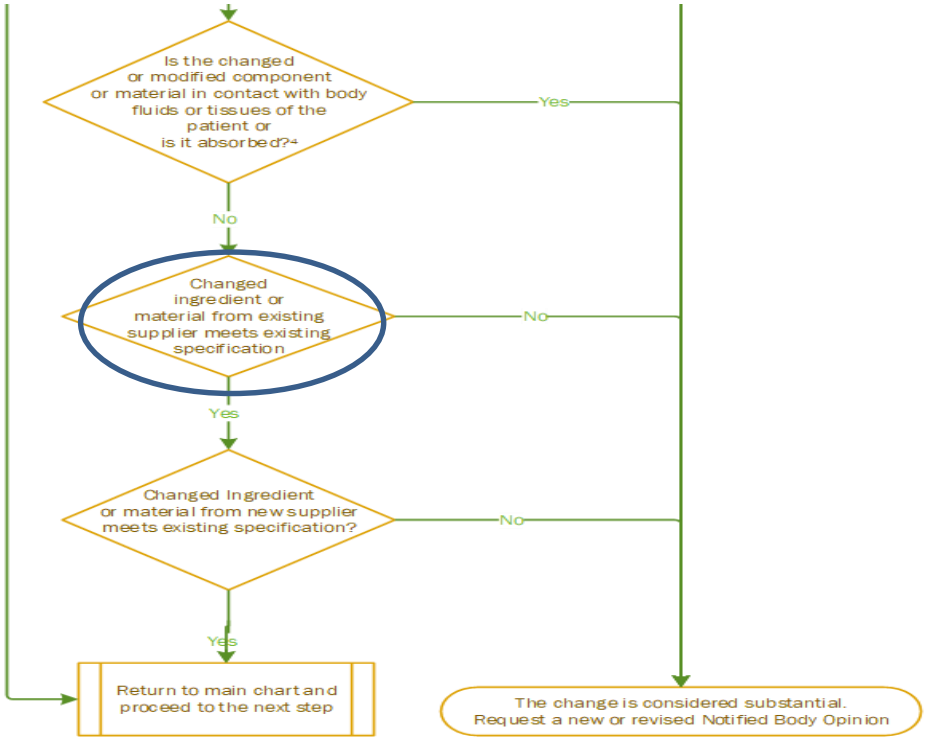

Examples

4.

Note: fifth diamond:

- *Changed ingredient or material from existing supplier meets existing specifications = not clear from detail given, more information must be supplied to make this determination*

- *If new material meets existing specifications, then change is* non substantial

- *If new material does not meet existing specifications, then change is* substantial

Examples

5.

Efpia: Minor design enhancement to prefilled pen device component.

Note:

Too little detail to determine substantial/ non-substantial.

If this would be a cosmetic change e.g. of the outer wings of a PFS this is likely to be a non-substantial change.