Updates to GN-21: Change Notification of Registered Medical Devices

Medical Devices Branch

28th March 2019

Industry Feedback

- Different terms used for document requirements across the regulatory guidances GN-15, GN-17, GN-18 and GN-21 may have led to some confusion
  - Examples: Preclinical validation, design validation and verification, design validation studies, clinical report/studies, clinical evidence

- Unsure on the type of documents to be submitted for each document requirement

- Some common questions received:
  - What type of documents will fall under the document category of ‘design verification and validation/ preclinical validation’?
  - What type of documents should be submitted for changes to software?
  - What type of documents are required as evidence for biological safety data?
  - What documents should be submitted for addition of models?
  - What documents should be submitted for change in manufacturing site name with no change to location and manufacturing process?

Overview

- Scope of changes in GN-21

- Editorial changes
  - Alignment of terms
  - Examples on type of documents

- Clarification on CN document requirements
  - Software
  - Biological materials
  - Addition of models

- Case studies

Scope of Changes

- Main updates to GN-21 Annex 1 Change Notification Submission Requirements

- **No changes** to overall document requirements for CN/ CN routes

- Updates in GN-21 will be indicated by R4.5 ►……..◄

Editorial Changes

Alignment of Terms

- Standardized terms used for document requirements across GN-15, GN-17, GN-18 and GN-21 to minimise confusion
  - Example: design verification and validation documents, clinical evidence

- Standardized examples
  - For example under ‘Proof of Quality Systems Management certificates’ for manufacturing/ sterilisation sites, the various acceptable documents are:
    - ISO 13485 certificate
    - Conformity to US FDA Quality Systems Regulations
    - Conformity to Japan MHLW Ordinance 169

Examples on Type of Documents

- Further elaboration on examples of the type of documents required for certain document requirements.
  - Example: Design validation and verification documents

	3. Changes in Materials in a General Medical Device			
	3A	3Bi	3Bii	3C
	B - Notification C and above - Technical	B - Notification C and above - Technical	B-D: Notification	B - NA C and above - Technical
Documentary Requirements:	All changes in type, source, processing and/or supplier of biological materials (including cells, tissues and/or derivatives of animal, human, microbial or recombinant origin) without a change in the intended purpose of the biological material.	All changes in material or material formulation (of non-biological origin) including changes to device coating or surface modification techniques that is intended to make direct/indirect contact with body tissues and fluids or is absorbed by the body, with no change in device performance specifications.	Unless the material has been reviewed in a previous device application and the new material has the same nature of body contact and contact duration.	All changes to materials that are used for shielding in medical devices emitting ionising radiation.
Design verification and validation documents	✓ (e.g. biocompatibility)	✓ (e.g. biocompatibility, mechanical)	✓ (e.g. biocompatibility, mechanical testing, sterilisation validation)	✓ (e.g. radiation safety validation report summary)

Clarification on CN document requirements

Software Document Requirements

- **Updated table** for further elaboration on document requirements for software changes submitted under different CN routes

Documentary Requirements	**Software change** (Notification)	**Software change** (Technical/ Review)
Detailed summary of software changes (can be included in the Annex 2, Summary Table of Change). To include information on the incremental changes or revisions to the software from the registered software version.	✓	✓
An overview of all verification, validation, and testing performed for the software both in-house and in a simulated or actual user environment prior to final release.		✓
All unresolved anomalies in the release version of the software should be summarized, along with a justification for acceptability (i.e. the problem, impact on safety and effectiveness, and any plans for correction of the problems).		✓
Evidence to demonstrate that the software issue has been resolved.		✓ (e.g. test cases verification)

Biological Document Requirements

- For changes to biological materials in devices, further elaboration on documentary requirements has been indicated.

Documentary Requirements:	**3. Changes in Materials in a General Medical Device**			
	3A	**3Bi**	**3Bii**	**3C**
	B - Notification C and above - Technical	B - Notification C and above - Technical	B-D: Notification	B - NA C and above - Technical
	All changes in type, source, processing and/or supplier of biological materials (including cells, tissues and/or derivatives of animal, human, microbial or recombinant origin) without a change in the intended purpose of the biological material.	All changes in material or material formulation (of non-biological origin) including changes to device coating or surface modification techniques that is intended to make direct/indirect contact with body tissues and fluids or is absorbed by the body, with no change in device performance specifications.	Unless the material has been reviewed in a previous device application and the new material has the same nature of body contact and contact duration.	All changes to materials that are used for shielding in medical devices emitting ionising radiation.
R4.5 ►Design verification and validation documents ◄	✓ (e.g. biocompatibility)	✓ (e.g. biocompatibility, mechanical)	✓ (e.g. biocompatibility, mechanical testing, sterilisation validation)	✓ (e.g. radiation safety validation report summary)
R4.5 ►Clinical Evidence (If applicable) ◄	✓	✓		✓
Biological safety data R4.5 ►Biological safety data - Process validation results to substantiate that manufacturing procedures are in place to minimize biological risks, in particular, with regard to viruses and other transmissible agents. This also includes inactivation of infection organisms. ◄	✓ (e.g. viral validation report)			

Addition of Models – document requirements

- For device description of the added model: A comparison, preferably in a table, of the design, specifications, intended use/indications for use between the current registered devices and the proposed added device(s) the proposed. To include labelled pictorial representation (diagrams, photos, drawings) where necessary.

- For device description of the added model: Justification for addition of device models to be grouped within the registered listing [e.g. Patient information leaflet and promotional material (including brochures and catalogues)].

Addition of Models – document requirements

- For marketing history: List of countries from HSA's reference regulatory agency jurisdictions where the medical device is marketed. Date (accurate to MMYYYY) and country where the device was first introduced for commercial distribution globally.)

  **Applicants may wish to provide the marketing history of the proposed added model(s) to assist with the evaluation process.*

- For AE/FSCA: To include a summary of reportable AEs and FSCAs for the MD since its first introduction on the global market. If there have been no AEs or FSCAs to date, provide an attestation from product owner on company letterhead, that there have been no AEs or FSCAs since commercial introduction of the device globally.

Case Studies

Case study 1: Addition of models

- Company ABC would like to submit CN for addition of model for ABC urinary catheters <Class B>. The proposed added model falls under change category 6Ai <addition of new medical devices to a device listing>

- List of registered models: XXX (sz 8), and YYY (sz 10)

- Proposed added model: ZZZ (sz 12)

Case study 1: Addition of models

- Taking reference from the revised Annex 1 to GN-21, the list of required documents will be:
  - Annex 2 LOC with the new model highlighted
  - Device description
  - Comparison table of the proposed added model with the already registered models
  - Justification for addition of the model to be grouped with already registered models
  - Device labelling (with changes highlighted/ identified)
  - DOC, LOA
  - Design verification and validation documents
  - Clinical evidence
  - Risk analysis
  - Proof of reference agency approvals
  - Marketing history* and AE/ FSCA Summary
  - Manufacturing information
  - Proof of QMS

*Applicants may wish to provide this additional document to assist with the evaluation process.

Case study 1: Addition of models

Document Requirements	Example(s)/ Elaboration
Annex 2 LOC	Annex 2 LOC in Microsoft excel format with new model highlighted/ indicated for addition. Template available at HSA website.
Device description	Example: Description of technical specifications of model ZZZ (French size, length, number of ports etc.)
Comparison table (between registered models and the proposed added model)	Comparison to be done to showcase similarities and differences in technical/ performance specifications/ product features/ functionalities
Justification for addition of model to be grouped with registered models	Grouping term used (e.g. FAMILY) Grouping criteria met: *may submit brochures/ catalogues
Device labelling (with changes highlighted/ indicated)	Redlined product IFU/ labels

Case study 1: Addition of models

Document Requirements	Example(s)/ Elaboration
Declaration of conformity	EU/ AU/ SG DOC are acceptable Template for SG DOC available at HSA website.
LOA	Template for LOA contained in GN-15 at HSA website
Design validation and verification documents	Biocompatibility Bench-testing Sterilisation Shelf-life validation <includes packaging/ functional validation> ***if not conducted, to provide justification**
Clinical evidence (if applicable)	Will be required to support novel technology and claims Literature review and/ or clinical studies

Case study 1: Addition of models

Document Requirements	Example/ Elaboration
Risk analysis (if applicable)	If there are updates performed to the risk management report to include assessment of the added model (i.e. additional risks/ new mitigation measures were identified), the updated report should be provided.
Proof of reference agency approval (s)	US FDA 510(k), Health Canada certificate, EU CE certificate, Australia TGA certificate, translated English copy of Japan MHLW certification.
Marketing history*	List of countries from HSA's reference regulatory agency jurisdictions where the medical device is marketed. Date (accurate to MMYY) and country where the device was first introduced for commercial distribution globally.)

*Applicants may wish to provide this additional document to assist with the evaluation process.

Case study 1: Addition of models

Document Requirements	Example(s)/ Elaboration
AE/ FSCA Summary	Provision of attestation of history of AE/ FSCAs since first commercial introduction. AE: issue, date and frequency of occurrence FSCA: date of occurrence, issue, countries affected, status of FSCA (open/ closed)
Manufacturing information	Indicate the physical manufacturing/ sterilisation sites
Proof of QMS	- ISO 13485 certificate - Conformity to US FDA Quality Systems Regulations - Conformity to Japan MHLW Ordinance 169

Case study 2: Change in manufacturing site information

- Company ABC would like to submit CN for **a change in name of manufacturing site** with no changes to the manufacturing site's address and no changes to specifications of the registered MD (blood pressure monitor/ Class B).

- The proposed added model falls under change category 1A <all changes to manufacturing facilities with no changes to specification of a registered MD>.

- The original manufacturing site AAA located at 10 Sunnyvale Drive, California 00001, USA, will now be renamed to site BBB with no change in the address.

- The product owner has confirmed that the manufacturing processes will be the same and there will be no change to the device specifications.

Case study 2: Change in manufacturing site information

Document Requirements	Example(s)/ Elaboration
Proof of QMS	Updated ISO 13485 certificate indicating the new manufacturing site name
Device labelling with changes highlighted/ identified	Only needs to be provided if there is a change in device labelling (e.g. when the manufacturing site is indicated on labels and the labels are updated as a result of the change in site).
Declaration from product owner on company letterhead to state that there is no change to device in all aspects, including intended use, technical specifications and/or sterilisation process	As MD is non-sterile, the declaration letter only needs to indicate that there is no change to device in all aspects, including intended use, technical specifications
Sterilisation validation report (including EO residuals report if applicable) and evidence of on-going sterilisation validation.	NA since devices are supplied as non-sterile

Case study 3: Change in notified body (for MDs approved in EU)

- Company ABC has been informed by their product owner that there would be a change in notified body for their registered thermometers.
- The thermometers had been approved for product registration previously with EU approval, under notified body AAA. Due to Brexit, the product owner has decided to switch to notified body BBB.
- There is no change in device specifications. However, due to the change in notified body, the device labelling would be amended.
- Company ABC's question is would they need to submit CN and if so, under which CN route?

Case study 3: Change in notified body (for MDs approved in EU)

- Under GN-21, this would fall under one of the scenarios which **do not** require CN submission

2.3. Changes which do not require Submission of Change Notification

The following specified change(s) would not require the submission of Change Notification to HSA:

- Labelling changes that only involve changes in layout, colour, font sizes and design, without change in prominence of precautions, warnings and contraindications.
- Labelling changes that involve the addition and/or removal of languages not required by the Authority.
- Labelling changes that involve the addition/removal of reference agency approvals (e.g. CE Marking).

GN-21

- Release date for Revision 4.5 of GN-21 Guidance on Change Notification for Registered Medical Devices:

  1st week of April (2019)

- Guidance document will be uploaded at the MDB webpage: http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Medical_Devices/Overview/Guidances_for_Medical_Device_Registration.html

THANK YOU

Questions can be directed to the Medical Devices Branch via the webform at: https://crm.hsa.gov.sg/event/feedback