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

1 Introduction

The Medical Devices Directives require certain changes of the device or of the quality system to be notified to the Notified Body. The requirements differ slightly from Directive to Directive and from conformity assessment annex to conformity assessment annex.

The following table with horizontal "criteria for notification", "criteria for a new approval" and "criteria to be assessed" and, vertically the conformity assessment annexes shows the requirements of the various annexes of the medical device directive (details for directives 90/385/EEC and 98/79/EC see Appendix 1):

Conformity assessment annex	Criteria for notification	Criteria for a new (supplementary) approval	Criteria to be assessed
93/42 Annex II section 4.4	Any change~~s~~ made to the approved design	Changes could affect conformity with the essential requirements	Conformity with the requirements of the Directive
93/42 Annex III section 6	Any significant change made to the approved product	Changes may affect conformity with the essential requirements or with the conditions prescribed for use of the product	Conformity with the provisions of this Directive
93/42 Annex II section 3.4	Any plan for substantial changes to the quality system or the product range covered		Requirements referred to in Annex 3 section 3.2
93/42 Annex V section 3.4	any plan for substantial changes to the quality system		Requirements referred to in Section 3.2
93/42 Annex VI section 3.4	any plan for substantial changes to the quality system		Requirements referred to in Section 3.2

Despite the fact that the wordings are slightly differing between the various **product specific annexes**, the authorities assume that in all cases only those changes need to be notified which "could affect conformity with the essential requirements". If this is the case, there is also a need for a further approval. Thus the criterion on when a change notification has to take place is identical to the criterion on whether a further approval is needed. The criterion for approving the

change of the device is evidently the fulfilment of Essential Requirements applicable to the respective device and whether corresponding documentation has been updated correctly.

For the **quality system annexes**, the criteria for triggering a notification obligation are comparable. Basically, a notification is needed where there is a "substantial change" to the quality system. In all these cases the Notified Body has to act.

The Notified Body has

(a) to decide whether the changed quality system still fulfils the requirements of the respective conformity assessment annex. It is to be noted that these requirements are differing amongst the conformity assessment annexes. Accordingly, the Notified Body needs to differentiate between these Annexes when assessing which change might affect the fulfilment of the various requirements;

(b) also to assess whether changes to the quality system could affect the fulfilment of Essential Requirements by the devices manufactured under the quality system.

2 Definitions

2.1 Supplier [1]

Organisation or person that provides a product, a service or information, and which is outside of the QMS of the manufacturer.

Examples of supplier: Producer, distributor, retailer or vendor of a product, or provider of a service or information

For the purpose of this document, the 'product' supplied may be a 'process', e.g. a supplier may provide a sterilisation process.

Note 1: For the purpose of this document, Note 1 of EN ISO 9000 3.3.6 does not apply

Note 2: The term supplier may refer to a 'contractor' or 'subcontractor'. For the purposes of the document the terms are regarded as synonymous.

2.2 Subcontractor

See 2.1 Note 2

2.3 Critical supplier

A critical supplier is a supplier delivering materials, components, or services that may influence the safety or performance of the device [2].

Note In Commission Recommendation 2013/473/EU of 24 September 2013 on the audits and assessments performed by notified bodies in the field of medical devices instead of "critical" also the term "crucial" is used: subcontractors in charge of processes which are essential for ensuring compliance with legal requirements ('critical subcontractor') or a supplier of crucial components or of the entire devices (both: 'crucial supplier').

3 Steps of the manufacturer for the change assessment procedure

The manufacturer shall have documented the responsibilities and authorities throughout implementation of changes and have documented procedures and evidence for

- Need/wish to change the device, quality system or product range covered by the quality system
- Verification and validation to take the decision to effectively modify the product or the product range or the quality system related to its risk management process

- The need to update the technical documentation
- Definition of a change implementation plan to monitor the change stages and meet the regulatory requirements
- Determination whether the change is substantial or not
- Decision to implement the change taken and the timing of implementation (dependent on Notified Body review)
- Information given to the Notified Body about any substantial change
- Final implementation of the change.

It is recommended that manufacturers contact and discuss with their Notified Body about any questions related to the substantial or not substantial characteristic of the change in order to get a common understanding.

The manufacturer shall establish, maintain and apply a procedure for categorising and implementing any changes to the device design/type (including software) and/or quality system and/or product range as either substantial or not substantial.

The reporting system of the manufacturer for substantial changes must fulfil the subsequent criteria:

The manufacturer shall inform the Notified Body of the planned substantial changes as soon as possible without delay.

A notification of any substantial change in the design/devices as well as in the quality system shall include

- A brief description of the modifications compared to the approved design/devices or the approved quality system
- The reason and origin for the changes/modifications
- In the case of design/device changes, a statement on the relevance to the compliance with the essential requirements
- The technical data and documentation supporting above points.

Manufacturers shall maintain a current listing of devices covered by the certificate and update the Notified Body accordingly (see also [3]).

4 Steps of Notified Body for the change assessment procedure

The Notified Body shall have documented the responsibilities and authorities for each individual change process. It must be clear who has taken the various decisions once a planned change comes to the notice of the Notified Body.

Furthermore, the Notified Body must have documented procedures in place and operating. These shall sufficiently specify the Notified Body's assessment (complete/partial – on desk/site…). These procedures shall also cover the verification of the manufacturer's implementation of the following processes:

- Identification of a need/wish to change the device, quality system or product range covered by the quality system
- Determination whether the change is substantial or not
- Information given by the manufacturer to the Notified Body about any substantial change

- Verification and validation performed by the manufacturer to take the decision to effectively modify the product or the product range or the quality system related to its risk management process
- Definition of a change implementation plan to monitor the change stages and meet the regulatory requirements
- Decision to implement the change taken by the manufacturer and the timing of implementation (dependent on Notified Body review)

The review by the Notified Body of the manufacturer´s procedures (documentation and implementation) to define a change (substantial or not) and to inform the Notified Body is a required part of the initial, surveillance and renewal audits of the quality system.

The Notified Body has to check the manufacturer's procedure(s) for categorising, reporting and implementing any changes to the device design/type (including software) and/or quality system and/or product range as either "substantial" or not substantial.

Note: For quality system annexes the Notified Body shall – on a sampling basis within its surveillance audits – also review those changes considered by the manufacturer as non-substantial and which therefore have not been reported.

Where a substantial change is reported, the Notified Body shall define the appropriate action including:

- Contract review
- Update of the contract if needed
- Document assessment related to the product or complete re-assessment of the design dossier or the type examination dossier
- Document assessment related to the quality system, special audit or complete re-assessment of the quality system
- Update of the EC certificate or addenda if needed
- List of elements for which implementation has to be checked during the next audit

The Notified Body procedure is part of the assessment by the designating authority.

5 Criteria for "substantial" changes

The manufacturer must report to the Notified Body any plan of "substantial"[1] changes before implementation. In the different directives, the terminology used differs, e.g. "substantial" or "significant". In this document only the term "substantial" is used.

5.1 Product changes

(Relates to Directive 90/385/EEC Annex 2 section 4.4 and Annex 3 section 6; Directive 93/42/EEC Annex II section 4.4 and Annex III section 6; Directive 98/79/EC Annex III section 6.3, Annex IV section 4.4 and 4.5 and Annex V sections 6 and 6.1)

Product changes should be considered substantial if the change may affect

- The conformity with the essential requirements and/or
- The indications and/or contraindications and/or warnings determined by the manufacturer to be appropriate to ensure the clinical performance of the device.

[1] For details and different wordings please see Appendix 2.

When determining whether or not a particular product change is "substantial" following considerations should be made (the list is not exhaustive):

- Changes of the intended purpose and/or the performance specification of the device?
- Changes of the materials of the device?
- Changes of suppliers
- Are new hazards introduced which have not previously been addressed?
- Are risks associated with existing hazards affected?
- Does the change alter the details on intended use given in the design/type approval dossier submitted to the Notified Body?
- Does the change trigger a need to alter the indications or contraindications for use or warnings necessary to ensure safety and efficacy for the intended use of the device?
- Does the change mean that the device will have different end users or be used in a different manner?
- Does the change mean that the clinical data/performance evaluation data for the original device is not sufficient to assure conformity of the changed device with the required characteristics and performance?
- Is the change a direct result of actions taken related to concerns arising from Post Market Surveillance including incidents/recalls/complaints?
- Is the change driven by the development of the state of the art?
- Does the change relating to a manufacturing process, facility or equipment impact the product´s safety or performance?

5.2 Quality system changes

(Relates to Directive 90/385/EEC Annex 2 section 3.4 and Annex 5; Directive 93/42/EEC Annex II section 3.4, Annex V section 3, Annex VI section 3.4; Directive 98/79/EC Annex IV section 3.4 and Annex VII section 3.4)

Quality system changes should be considered substantial if (list is not exhaustive)

- The change affects compliance of the devices covered by the quality system with the essential requirements or the approved type/design
- The change affects the compliance of the quality system with its own regulatory requirements (e.g. if the manufacturer changes archiving from paper to electronic storage).

When deciding whether or not a particular quality system change is "substantial" the following considerations should be made:

- Does the change relating to a manufacturing process, facility or equipment impact the product´s safety or performance?
- Does the change affect the manufacturing technologies (processes and equipment)?
- Does the change affect the location of the manufacturer´s activity?
- Does the change affect product conformity with the essential requirements or the approved type/design (e.g. change of the supplier)?
- Does the change affect the arrangements implemented to achieve continued compliance of the quality system with the relevant harmonized standards and/or the requirements of the directive (e.g. design verification, design validation, organizational structure, process interaction, quality control procedures, addition or deletion or move of a facility)?
- Does the change affect the organization of the manufacturer?

5.3 Changes to the product range

(Relates to Directive 90/385/EEC Annex 2 Section 3.4 and Annex 5, Directive 93/42/EEC Annex II section 3.4, Annex V section 3.4 and Annex VI section 3.4 and Directive 98/79/EC Annex IV section 3.4 and Annex VII section 3.4)

For changes to the product range covered by the quality system, the change affects the subcategories or generic device groups of medical devices designed and/or manufactured through the quality system.

As the Notified Body has to assess the technical documentation on a representative basis depending on the subcategories or generic device groups this will directly influence this assessment. See also [4].

When considering whether or not a particular product-range change is "substantial" the following considerations should be made:

- Are there any additional or deleted subcategories or generic device groups of medical devices that are designed and manufactured through the quality system?

5.4 Particular cases, examples

In this section, particular cases are described to illustrate the principles explained above. In the headlines reference is made to which section(s) the examples belong or could belong.

Changes to design (general) (5.1)

Changes in design span the full spectrum from minor engineering changes to major changes in operating principles. All design changes must be evaluated, verified and validated according to the documented procedures accepted by the Notified Body.

Changes to build-in control mechanism (5.1, 5.2)

Almost all changes in the control mechanism of a device raise questions of safety and performance. Therefore, in most circumstances these changes are substantial.

Control mechanism is a mean of verifying or checking that the specifications or outputs of the device meet a standard or predetermined result. They are mechanisms put in place to maintain on-going control or regulate the output of a device.

Changes to operating principles (5.1, 5.2)

Similar to changes in the control mechanism, changes to the operating principles, including a change in the source of energy used by the device, usually are substantial. These changes are often accompanied by substantial changes to device labelling.

Operating principles are the means by which a device produces or brings about an intended or appropriate effect. They are the means whereby a device is able to have a certain influence on a person or its surroundings.

Changes to design specifications (5.1, 5.2)

Changes to the design specifications (including but not limited to change in expiration date, primary packaging or energy type), physical, dimensional, environmental specifications, ergonomics of patient user interface, may be substantial if they affect the indications for use or the performances of the device or raise new safety and performance issues.

If the response to any of the following questions is yes, then it is likely that the design change is substantial

1. Does the design change affect the indications or contraindications for use or warnings necessary to ensure safety and performance for the intended use of the device?
2. Are further clinical data necessary to support the safety and performance of the altered device?
3. Do the results of a risk analysis, undertaken during the design verification and validation process, raise new issues of safety and performance?
4. Does the change affect the performance of the medical device?

In cases where the change consists only of tightening of design specifications within specified tolerances and where there is no creation of new features, the change is not considered to be substantial.

Changes to software (5.1)

Many changes to a device's software will require an evaluation and acceptance by the Notified Body. The following would be considered substantial changes:

- a software change, which impacts the control of the device, that may alter the diagnosis or therapy delivered to the patient;
- an alteration in software that modifies an algorithm impacting the diagnosis or the therapy delivered;
- a software change that impacts the way data is read or interpreted by the user, such that the treatment or diagnosis of the patient may be altered when compared to the previous version of the software;
- a software change that replaces previously required user input to a closed loop decision;
- addition of a new feature to the software that may change the diagnosis or the therapy delivered to the patient;
- introduction to or removal of a new alarm function from the software such that a response to the new configuration may change the treatment of the patient in comparison to the previous version of the software;
- a software change that incorporates a significant change to the operating system on which the software runs.

If the software is modified to correct an error (for example, a change in algorithm), for which there is a safety risk to the patient if the error is not corrected, this software change may require an evaluation and approval by the Notified Body. In such instances and where the software change is a corrective or preventative action for a recall, consultation with the Notified Body is recommended to determine if the change requires an approval.

If a software change is only intended to correct an inadvertent logic error that does not pose a safety risk and brings the system back into specification, this is not a substantial change.

The following would not be considered substantial changes:

- a software change that only introduces non-therapeutic and/or non-diagnostic features such as printing, faxing, improved image clarity, reporting format or additional language support
- a software change that only modifies the appearance of the user interface with negligible risk of impacting the diagnosis or therapy delivered to the patient
- a software change that disables a feature that does not interact with other features

Changes to materials for medical devices or active implantable medical devices (5.1, 5.2)

Changes to the materials of a medical device or active implantable medical device may lead to subsequent changes, such as manufacturing processes, equipment, labelling or changes to the device performance specifications, and these must also be considered separately. The following changes should be considered:

(1) All changes to the sourcing or processing of materials of human origin or substances, which, if used separately, may be considered to be a medicinal product are considered substantial and need an approval of the Notified Body.

(2) For materials of animal origin : Changes of the geographical source of animals, the raw materials of animal origin, and the processes for selection, collection, handling, control and inactivation/elimination that may modify viral safety are considered substantial and need an approval of the Notified Body.

(3) For tissues (or derivatives) derived from species concerned by regulation (EU) No 722/2012: Changes regarding tissues (or derivatives), processes for selection, collection, processing, handling, inactivation and elimination or any new data collected by the manufacturer and relevant to the medical device with regard to TSE risk are considered substantial and need an approval of the Notified Body.

(4) Changes within a single generic material type or changes in formulation can affect the chemistry, metallurgy or other property, such as stability, of the device.

In each of the above instances, it must be determined if the device is a surgically invasive device intended to be absorbed by the body or to remain in the body for at least thirty consecutive days. If this is the case, and the altered material would be in contact with body tissues or fluids, then an approval of the Notified Body is required.

Even when the material would not be in contact with body tissues and fluids, the question of design specifications arises. If changes to the design specifications are required, they should be done according to section ”Change to design” above.

In cases where devices are not intended to be absorbed by the body or to remain in the body for at least 30 consecutive days, but where the altered material is in contact with body tissues or fluids an approval by the Notified Body is required unless the new material meets the existing specifications. As in other cases, changes to performance specifications must be considered as described in section ”Changes to design” above.

If the supplier of the material is a crucial supplier (definition see [5]), that change is substantial. If the supplier or vendor of the material changes, but the material meets the manufacturer's previously reviewed specifications and acceptance criteria, with the exception of human or animal derived materials, then that change is not substantial.

Changes to materials for in vitro diagnostic devices (5.1, 5.2)

There is a distinction between IVD devices and other devices with regard to material changes. This section also considers changes to the method used for IVD device (IVDD).

Changes to materials in an IVDD often affect its performance characteristics, including specificity or sensitivity, and would be assessed as to their impact on the safety and performance of the device.

Changes to materials that necessitate the testing of additional clinical samples to determine the performance characteristics of the IVDD would be considered a substantial change, unless the additional clinical testing only confirms that the altered IVDD still conforms to the certified performance specifications and no labelling changes are necessary.

Changes to the materials of an IVDD that result in a change to the operating principle of the product (for example, change from Immunofluorescence to ELISA) are considered substantial and require approval by the Notified Body.

Changes to materials that potentially affect the operating principle of an IVDD include changes in reaction components or materials such as calibration materials, or changes in methods such as specimen pre-treatment, incubation times and temperatures. If these changes result in altered performance characteristics that are reflected in the labelling, then an approval by the Notified Body is required.

Changes to labelling (5.1, 5.2)

Changes to a device, including changes to performance specifications and materials, often lead to labelling changes. Labelling changes also occur in response to changing user requirements.

Each labelling change must be considered separately.

Changes to the intended use or indications for use will require an approval by the Notified Body unless the changes are within the already approved set of indications. Changes within an approved set of indications should be evaluated at surveillance audit. However, if a limitation to the indications for use is introduced as a result of concerns associated with the safe and effective use of the device, a contraindication must be added. This is considered a substantial change.

The deletion of a contraindication, such as "not for paediatric use" is considered a substantial change and requires an approval by the Notified Body.

Minor changes to clarify the existing wording of the warnings and precautions for a device may not trigger the need for approval. However, in the case where these changes add or remove a contraindication, or remove a warning or precaution, an approval by the Notified Body is required.

Changes made to device labelling solely for the purposes of clarifying instructions in order to make the device easier, safer or more effective to use will not require an approval by the Notified Body. For example, device labelling often requires modifications in language and structure to be used by a lay person. Provided no changes are made in the indications for use, these changes are not substantial.

Changes to labelling to include additional languages required in other regulatory jurisdictions are not substantial.

A change in the shelf life is considered a substantial change, and an approval by the Notified Body is required, when the protocols and methods for determining shelf life have been changed or have not been reviewed in a previous approval.

Changes to manufacturing processes, facility or equipment (5.1, 5.2)

A change to the manufacturing process, facility or equipment that affects the safety or performance of a device is substantial. For example, this may include changes to the packaging process, which is a component of manufacturing.

In cases where the manufacturer´s name and address on the device labelling stays the same but a new manufacturing facility is added or production facilities are moved, the new or moved facility will need to be covered by the Notified Body's quality management certification.

When a critical supplier´s manufacturing process, facility or equipment changes, this is normally substantial unless otherwise justified.

Changing a test acceptance criterion or test method or removal of test acceptance criteria, in-process inspection, or final inspection is considered substantial (5.1 only).

Changes to sterilization (5.1, 5.2)

Changes in sterilization procedures are often considered to be substantial.

The nature of sterilization is such that it is impossible to determine by inspection and testing if the sterilization of the actual device(s) has been successful. Medical devices are considered sterile if manufacturers can demonstrate a sterility assurance level (SAL) of 10-6 or better. The sterilization process needs to be verified and validated and its performance routinely monitored. For this reason the notified body shall require documentation pertaining to changes in sterilization method or process for medical devices or any changes that might affect the effectiveness of the process.

Such changes include but are not limited to:

- Changes that increase the bioburden alert or action levels or that introduces an organism that is more difficult to kill
- Changes in manufacturing location
- Device design and material changes that introduce a feature that is more difficult to sterilize
- Changes in sterilization process or equipment or cycle parameter
- Change of sterilization service provider
- Changes in the density or configuration of the sterilization load
- Changes to the quality control verification and validation process such as introducing parametric release
- Reductions in conventional incubation durations

This rationale also applies to changes in the packaging of medical devices subject to sterilization. In general, any change to the sterilization method or process of a medical device, or a change to the packaging for the sterilization of a medical device is considered to be a substantial change. Changes in packaging characteristics of a sterile medical device, configuration or density could affect the absorption or penetration of the sterilant, the residue levels (where applicable) and the effectiveness of the sterilization process in addition to the safety of the sterile device. Issues of compatibility between the packaging material and the sterilization process must also be taken into consideration to ensure that seal integrity is not affected and that the packaging preserves the functionality and safety of the device throughout its declared shelf-life.

Examples for substantial changes (5.1, 5.2)

a) to EC-approved medical devices design/type (including software) (MDD Annexes II, 4.4 and III; IVDD Annexes VI-4.2 and V, respectively)

- Changes to the medical device included computer software (e.g. new functionalities, new algorithms for computing) which will change the specifications and/or performance of the device (e.g. changes of those materials which have to be biocompatible or changes of main components like power source, Central Processing Unit (CPU), defibrillator-capacitors etc.)
- New operating system
- Change in material supplier that potentially affects biocompatibility (ER 7)
- Change of the sterilisation method or in sterilization cycle that potentially affects sterilization validation and sterility (ER 8)
- Change in the diameter/French size) of a catheter that potentially affects the flow rate and thus performance (ER 7)
- Change in the packaging configuration that affect protection against transportation or that might affect maintenance of sterility during shelf life (ER 5, 8)

- Change in the design of a product, that leads to new specifications and affects the essential requirements (e.g. ER 7, 11,12)
- Other changes which affect the design, performance/characteristics of the device, or safety (e.g. new welding method, or in the case of computer software, new functionalities, new algorithms for computing, new operating system) are considered to be substantial changes.

Note: In the case of IVD reagents substantial changes are those which could significantly influence the performance characteristics compared to those of the originally approved design. Where changes of the performance characteristics are due to changes of the manufacturing process, these may well be considered as substantial.

b) of changes to EC-approved quality systems (MDD Annex II.3, V, VI; IVDD Annexes IV and VII respectively):

- Change of a critical material supplier; critical component/process subcontractor
- A change in the manufacturing process whereby a new technology is introduced
- Buying a product design from a subcontractor, that falls within the manufacturers own approved product range, but which was not designed under the manufacturer´s own design control system
- Making substantial changes to the sterilization process/cycle that would necessitate a full new validation (e.g. going form EtO sterilization to gamma sterilization)
- Changing the sterilization contractor
- Building a new clean room or changing an existing cleanroom's classification
- Making substantial changes to the environmental monitoring program or then environmental control systems
- Moving a production line from in-house to an outside facility (manufacturer´s own or a contractor); introducing a production line into manufacturer´s own facility from an outside facility
- Making substantial changes to the structuring of the quality system

Examples for non-substantial changes (5.1, 5.2)

a) to EC-approved medical devices design/type (including software) (MDD Annexes II, 4.4 and III; IVDD Annexes VI-4.2 and V, respectively)

- A change in the length of the proximal end of a central venous catheter does not necessarily affect performance (ER 7)
- A change in the labeling layout
- A change in the design of the product that does not alter the design specifications, but is only made to get better tolerances for a certain specification does not necessarily affect performance (ER 7), so is not considered as substantial change
- A change in a manufacturing process that will need process validation, but does not affect the product specifications including tolerances, does not necessarily affect performance (ER 7), so is not considered a substantial change

b) of changes to EC-approved quality systems (MDD Annex II.3, V, VI; IVDD Annexes IV and VII respectively):

- Addition of an electrical components supplier, e.g. for resistors, to the list of approved suppliers
    - Selection and approval of suppliers is part of the quality management system of the manufacturer

- The components to be supplied
  - Meet the manufacturer´s existing specifications
  - Do not fall within the manufacturer´s classification of a "substantial change".

6 References and Sources

References

90/385/EEC[2]

93/42/EEC[3]

98/79/EC[4]

Commission Regulation (EU) No 722/2012[5]

Sources

[1] NBOG BPG 2010-1: Guidance for Notified Bodies auditing suppliers to medical device manufacturers

[2] GHTF SG4/N33R16: 2007 Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 3: Regulatory Audit Reports

[3] NBOG BPG 2010-3: Certificates issued by Notified Bodies with reference to Council Directives 93/42/EEC, 98/79/EC, and 90/385/EEC, General comments, No. 5

[4] NBOG BPG 2009-4: Guidance on Notified Body's Tasks of Technical Documentation Assessment on a Representative Basis

[5] Commission Recommendation 2013/473/EU from 24.09.2013 on the audits and assessments performed by notified bodies in the field of medical devices

[6] EN ISO 13485:2012 Medical devices – Quality management systems – Requirements for regulatory purposes

[7] EN ISO 9000: 2005 Quality management systems – Fundamentals and vocabulary, Clause 3.3.6

[8] GHTF/SG4/N28R4: 2008 Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers Part 1: General Requirements

[9] GHTF SG4/N30: 2010 Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 2: Regulatory Auditing Strategy

[2] Directive 90/385/EEC on Active Implantable Medical Devices, O.J. L 189, 20.7.1990, p. 17, as amended

[3] Directive 93/42/EEC on Medical Devices, O.J. L 169, 12.7.1993, p. 1, as amended

[4] Directive 98/79/EC on *in vitro* diagnostic Medical Devices, O.J. L 331, 7.12.1998, p. 1, as amended

[5] Commission Regulation (EU) No 722/2012 concerning particular requirements as regards the requirements laid down in Council Directives 90/385/EEC and 93/42/EEC with respect to active implantable medical devices and medical devices manufactured utilising tissues of animal origin, O.J. L 212, 9.8.2012, p. 3

[10] GHTF SG3/N17: 2008 Quality management system – Medical devices – Guidance on the control of products and services obtained from suppliers

[11] GHTF SG4/N84: 2010 Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 5: Audits of manufacturer control of suppliers

[12] Recommendation NB-MED/2.5.2/Rec 2: 2008: Reporting of design changes and changes of the quality system

[13] Health Canada: 2011: Guidance for the Interpretation of Significant Changes

Keywords critical/crucial supplier, critical subcontractor, notified body, reporting, significant changes, substantial changes

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Appendix 1 – Notification requirements in 90/385/EEC and 98/79/EC

In addition to table 1 the following table with horizontal "criteria for notification", "criteria for a new approval" and "criteria to be assessed" and, vertically the conformity assessment annexes shows the requirements of the various annexes of the active implantable and *in vitro* medical device directive:

Conformity assessment annexes of the directives	**Criteria for notification**	**Criteria for a new (supplementary) approval**	**Criteria to be assessed**
90/385 Annex 2 section 4.4	Any modification made to the approved design	Modifications may affect conformity with the essential requirements	Compliance with the requirements of the Directive
90/385 Annex 3 section 6	Any modification made to the approved product	Modifications may affect conformity with the essential requirements or with the conditions of use specified for the product	Satisfy the essential requirements
90/385 Annex 2 section 3.4	Any plan to alter the quality system		Requirements referred to in Annex 3 section 3.2
90/385 Annex 5	Any plan to alter the quality system		Requirements referred to in Annex 3 section 3.2
98/79 Annex III section 6.3	Any significant change made to the approved design	Changes could affect conformity with the essential requirements of the Directive or with the conditions prescribed for use of the product	Conformity with the design-related requirements of the Directive
98/79 Annex IV section 4.4	Any changes made to the approved design	Changes could affect conformity with the essential requirements of the Directive or with the conditions prescribed for use of the device	Conformity with the requirements of the Directive

Conformity assessment annexes of the directives	Criteria for notification	Criteria for a new (supplementary) approval	Criteria to be assessed
98/79 Annex IV section 4.5	Any changes to the pathogen and markers of infections to be tested, in particular as a consequence of biological complexity and variability		Conformity with the requirements of the Directive
98/79 Annex V section 6	Any changes to the pathogen and markers of infections to be tested, in particular as a consequence of biological complexity and variability.		Meet the essential requirements of this Directive
98/79 Annex V section 6.1	Any changes to the approved device	Wherever the changes may affect conformity with the essential requirements of the Directive or with the conditions prescribed for use of the device	Meet the essential requirements of this Directive
98/79 Annex IV section 3.4	Any plan for substantial changes to the quality system or the product-range covered		Requirements referred to in section 3.2
98/79 Annex VII section 3.4	Any plan for substantial changes to the quality system		Requirements referred to in section 3.2

For wording in Commission Regulation (EU) No 722/2012 see Appendix 2.

Appendix 2 – Relevant parts of the directives

Annex 2 of Directive **90/385/EEC**:

3. Quality system

3.4. The manufacturer shall inform the notified body which has approved the quality system of **any plan to alter the quality system**.

The notified body shall evaluate the proposed modifications and shall verify whether the quality system so modified would meet the requirements referred to in 3.2; it shall notify the manufacturer of its decision. This decision shall contain the conclusions of the control and a reasoned evaluation.

4. Examination of the design of the product

4.4. The applicant shall inform the notified body which issued the EC design examination certificate of **any modification made to the approved design**. Modifications made to the approved design must obtain supplementary approval from the notified body which issued the EC design examination certificate where such modifications may affect conformity with the essential requirements of this Directive or the conditions prescribed for the use of the product. This supplementary approval shall be given in the form of an addendum to the EC design examination certificate.

Annex 3 of Directive **90/385/EEC**:

6. The applicant shall inform the notified body which issued the EC type-examination certificate of **any modification made to the approved product**.

Modifications to the approved product must receive further approval from the notified body which issued the EC type-examination certificate where such **modifications may affect** conformity with the essential requirements or with the conditions of use specified for the product. This new approval shall be issued, where appropriate, in the form of a supplement to the initial EC type-examination certificate.

Annex 5 of Directive **90/385/EEC**:

3. Quality system

3.4. The manufacturer shall inform the notified body which has approved the quality system of **any plan to alter that system**.

The notified body shall evaluate the proposed modifications and shall verify whether the quality system so modified would meet the requirements referred to in 3.2; it shall notify the manufacturer of its decision. This decision shall contain the conclusions of the control and a reasoned evaluation.

Annex II of Directive **93/42/EEC**:

3. Quality system

3.4. The manufacturer must inform the notified body which approved the quality system of **any plan for substantial changes to the quality system or the product-range covered**. The notified body must assess the changes proposed and verify whether after these changes the quality system still meets the requirements referred to in Section 3.2. It must notify the manufacturer of its decision. This decision must contain the conclusions of the inspection and a reasoned assessment.

4. Examination of the design of the product

4.4. **Changes to the approved design** must receive further approval from the notified body which issued the EC design-examination certificate wherever the changes could affect conformity with the essential requirements of the Directive or with the conditions prescribed for use of the product. The applicant shall inform the notified body which issued the EC design-examination certificate of any such changes made to the approved design. This additional approval must take the form of a supplement to the EC design-examination certificate.

Annex III of Directive **93/42/EEC**:

6. The applicant must inform the notified body which issued the EC type examination certificate of **any significant change** made to the approved product.

Changes to the approved product must receive further approval from the notified body which issued the EC type-examination certificate wherever the **changes may affect** conformity with the essential requirements or with the conditions prescribed for use of the product. This new approval must, where appropriate, take the form of a supplement to the initial EC type examination certificate.

Annex V of Directive **93/42/EEC**:

3. Quality system

3.4. The manufacturer must inform the notified body which approved the quality system of any plan for **substantial changes** to the quality system. The notified body must assess the changes proposed and verify whether after these changes the quality system still meets the requirements referred to in Section 3.2. After the abovementioned information has been received the decision is notified to the manufacturer. It must contain the conclusions of the inspection and a reasoned assessment.

Annex VI of Directive **93/42/EEC:**

3. Quality system

3.4. The manufacturer must inform the notified body which approved the quality system of **any plan for substantial changes** to the quality system.

The notified body must assess the changes proposed and verify whether after these changes the quality system will still meet the requirements referred to in Section 3.2.

After receiving the abovementioned information it must notify the manufacturer of its decision. This decision must contain the conclusions of the inspection and a reasoned assessment.

Annex III of Directive **98/79/EC**:

6. For devices for self-testing the manufacturer shall lodge an application for examination of the design with a notified body.

6.3. The applicant shall inform the notified body which issued the EC design examination certificate of any significant change made to the approved design. **Changes to the approved design** must receive further approval from the notified body which issued the EC design-examination certificate wherever the changes could affect conformity with the essential requirements of the Directive or with the conditions prescribed for use of the product. This additional approval shall take the form of a supplement to the EC design-examination certificate.

Annex IV of Directive **98/79/EC**:

3. Quality system

3.4. The manufacturer must inform the notified body which approved the quality system of **any plan for substantial changes to the quality system or the product-range covered**.

The notified body must assess the changes proposed and verify whether after these changes the quality system still meets the requirements referred to in section 3.2. It must notify the manufacturer of its decision. This decision must contain the conclusions of the inspection and a reasoned assessment.

4. Examination of the design of the product

4.4. **Changes to the approved design** must receive further approval from the notified body which issued the EC design-examination certificate wherever the **changes could affect** conformity with the essential requirements of the Directive or with the conditions prescribed for use of the device. The applicant shall inform the notified body which issued the EC design-examination certificate of any such changes made to the approved design. The additional approval must take the form of a supplement to the EC design-examination certificate.

4.5. The manufacturer shall inform the notified body without delay if it has obtained information **about changes to the pathogen and markers of infections** to be tested, in particular as a consequence of biological complexity and variability. In this connection, the manufacturer shall inform the notified body whether any such change is likely to affect the performance of the *in vitro* diagnostic medical device concerned.

Annex V of Directive **98/79/EC**:

6. The manufacturer shall inform the notified body without delay if it has obtained information about **changes to the pathogen and markers of infections** to be tested, in particular as a consequence of biological complexity and variability. In this connection, the manufacturer shall inform the notified body whether **any such change** is likely to affect the performance of the in vitro device concerned.

6.1. **Changes to the approved device** must receive further approval from the notified body which issued the EC type-examination certificate wherever the changes may affect conformity with the essential requirements of the Directive or with the conditions prescribed for use of the device. The applicant shall inform the notified body which issued the EC type-examination certificate of any such change made to the approved device. This new approval shall take the form of a supplement to the initial EC type-examination certificate.

Annex VII of Directive **98/79/EC**:

3. Quality system

3.4. The manufacturer shall inform the notified body which approved the quality system of **any plan for substantial changes to the quality system**.

The notified body must assess the **changes proposed** and verify whether after these changes the quality system still meets the requirements referred to in section 3.2. It must notify the manufacturer of its decision. This decision must contain the conclusions of the inspection and a reasoned assessment.

Commission Regulation (EU) No. **722/2012** – Medical Devices incorporating products of animal origin:

Article 5

7. The **manufacturer shall collect, evaluate and submit to the notified body information regarding changes** with regard to the animal tissue or derivatives used for the device or with regard to the TSE risk in relation to the device. Where such information leads to an increase of the overall SE risk, the provisions of paragraphs 1-6 are applicable.

Annex I 1.2. Process of risk assessment

At a minimum, the manufacturer must consider the following key steps:

(a) selecting starting materials (tissues or derivatives) considered appropriate regarding their potential contamination with TSE infectious agents (see 1.2.1, 1.2.2, 1.2.3 and 1.2.4) taking into account further collection, handling, transport, storage and processing;

(b) applying a production process to remove or inactivate TSE infectious agents on controlled sourced tissues or derivatives (see 1.2.5);

(c) **maintaining a system to collect and evaluate production and post-production information regarding changes which may affect** the assessment of the suitability of steps referred to in points (a) and (b)

Annex I 2.1 Information of the Notified Body regarding changes and new information

Any change in relation to processes of sourcing, collection, handling, processing and inactivation or elimination **and any new information** on TSE risk collected by the manufacturer and relevant for the medical device that could modify the result of the manufacturer's risk assessment must be transmitted to the notified body and, where applicable, needs to be approved by the notified body prior to its implementation.