Expert Commentary on BS EN ISO 13485:2016, *Medical devices – Quality management systems – Requirements for regulatory purposes*

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Summary

The third edition of ISO 13485 was published on 1 March 2016 and has been adopted as EN ISO 13485:2016. The European adoption has identical requirements in the body of the standard and the addition of a European Foreword and European Annexes ZA, ZB and ZC, which describe the relationship between the requirements of the three European Medical Devices Directives and the clauses of the standard. ISO 13485:2016 is a revision of the second edition of ISO 13485, which was published in 2003. An updated European adoption of the second edition was published in 2012 with a revised European Foreword and new Annexes ZA, ZB and ZC. The third edition of the standard has been put forward to be harmonized against the Active Implantable Medical Devices Directive (AIMD) 90/385/EEC (as amended), the Medical Devices Directive (MDD) 93/42/EEC (as amended) and the In Vitro Diagnostic Medical Devices Directive (IVDD) 98/79/EC, and has revised Annexes ZA, ZB and ZC with more detail, as compared with the Annexes Z for the 2012 version of EN ISO 13485, and changes to reflect the revised content of ISO 13485.

The structure of ISO 13485:2016 is aligned with ISO 9001:2008 and follows the clause and subclause sequence in ISO 9001:2008, but with some adjustment to the subclause numbering. This adjustment was introduced to accommodate the classification system for observations described by the Global Harmonization Task Force (GHTF)[1] and used in the pilot Medical Devices Single Audit Programme (MDSAP),[2] established by some members of the International Medical Devices Regulators Forum (IMDRF). The GHTF was a precursor organization to the IMDRF. This classification system is numerical with a greater classification being applied to repeat or multiple observations in the same three-digit subclause (e.g. 4.2.1). In ISO 13485:2016, the subclause numbering has been amended to make the content at the three-digit level applicable to discrete aspects of the quality management system and reduce the breadth of content in some of the three-digit subclauses by reducing the occurrence of four- and five-digit subclause numbers.

The structure of the revised ISO 13485 does not follow the structure of ISO 9001:2015[3] because:

1. the two standards were developed in parallel; and
2. ISO 13485 is used for regulatory purposes and there was not alignment at this time with the regulatory authorities to introduce a major restructure to this standard.

However, Annex B has been included in the standard to provide cross-references with the clause structure in ISO 9001:2015 for organizations that wish to comply with both standards.

Changes were introduced in this third edition of ISO 13485, based on a design specification approved by ballot in the ISO Technical Committee. This was in order to update the requirements in line with current regulatory expectations and foreseen future regulatory requirements, such as some of those proposed in the European Medical Devices Regulation and IVDD. In addition, experience in use of the 2003 edition of the standard was taken into account. The changes include:

- incorporation of risk-based approaches beyond product realization. Risk is considered in the context of the safety and performance of the medical device and in meeting regulatory requirements;

1. GHTF/SG3/N19:2012 – Nonconformity Grading System for Regulatory Purposes and Information Exchange http://www.imdrf.org/docs/ghtf/final/sg3/technical-docs/ghtf-sg3-n19-2012-nonconformity-grading-121102.doc
2. http://www.imdrf.org/workitems/wi-mdsap.asp
3. ISO 9001:2015, *Quality management systems — Requirements*

- increased linkage with regulatory requirements, and in particular regulatory documentation;
- application to organizations throughout the lifecycle and supply chain for medical devices;
- harmonization of the requirements for software validation for different software applications (QMS software, process control software, software for monitoring and measurement) in different clauses of the standard;
- emphasis on appropriate infrastructure, particularly for production of sterile medical devices, and addition of requirements for validation of sterile barrier properties;
- additional requirements in design and development on consideration of usability, use of standards, verification and validation planning, design transfer and design records;
- emphasis on complaint handling and reporting to regulatory authorities in accordance with regulatory requirements, and consideration of post-market surveillance; and
- planning and documenting corrective action and preventive action, and implementing corrective action without undue delay.

Significant changes introduced by ISO 13485:2016

1. Scope (MODIFIED)

The scope has been rewritten to emphasize that the standard can be used by organizations involved in one or more stages in the lifecycle or the supply chain for a medical device. This clarifies that, as well as being used by organizations that place medical devices on the market under their own name (often referred to as the 'legal manufacturer'), the standard can be used by organizations that, for example:

- undertake part of the medical device lifecycle, such as design and development or repair and maintenance;
- are part of the supply chain for a medical device such as raw material, component, or subassembly or manufacture;
- provide services as part of the supply chain such as contract manufacture, sterilization, logistics or calibration; or
- are economic operators in the supply chain such as importer, distributor or authorized representative.

Additionally, changes in the scope clarify that:

- the requirements of standard are applicable irrespective of the size of the organization;
- certain requirements apply based on the type of medical device covered by the quality management system (QMS);
- certain requirements do not apply based on the role undertaken by the organization; and
- the QMS processes apply to the organization rather than the medical device.

Some information previously included in the scope has been relocated to the Introduction.

2. Normative references (MODIFIED)

ISO 13485:2016 has one normative reference and that is to ISO 9000 for definitions. However, the definitions of 'product' and 'risk' are not taken from ISO 9000:2015[4] and these are included as defined terms in ISO 13485:2015 (see Terms and definitions section).

4. ISO 9000:2005, *Quality management systems — Fundamentals and vocabulary*

3. Terms and definitions (MODIFIED)

A number of terms have been modified to align with the latest use in regulatory requirements. In particular, definitions from GHTF documents[5] have been used and the source of the definitions is added for reference. New definitions have been introduced for economic operators in the supply chain such as 'manufacturer', 'importer', 'distributor' and 'authorized representative'. Other new definitions that have been added to aid clarity in the use of the standard are: 'lifecycle'; 'medical device family'; 'performance evaluation'; 'post-market surveillance'; 'product', 'purchased product'; 'risk'; 'risk management'; and 'sterile barrier system'.

The definition of 'product' used in ISO 13485:2016 is that from the 2005 edition of ISO 9000, as the use of 'product' is as a collective term that encompasses hardware, software, processed materials and services. In the 2015 edition of ISO 9000, the definition of 'product' has been changed to only tangible materials, excluding services, and ISO 9001:2015 uses the term 'services' alongside 'product'. In ISO 13485, it is emphasized that the definition of 'product' includes services. When ISO 13485:2016 uses 'product' in a requirement, it can apply to raw materials, components, subassemblies, finished medical devices or services used by or supplied by the organization; when it uses 'medical device', it applies to the finished medical device only.

It should also be noted that ISO 13485:2016 includes the definition of risk taken from ISO 14971 rather than that used in ISO 9000:2015.

4. Quality management system (MODIFIED)

There have been a number of changes to the general requirements for the QMS, both in terms of content and layout.

The first major changes show the increased link to the inclusion of applicable regulatory requirements into the QMS, both in terms of a new requirement for the organization to document its role or roles under the regulatory requirements that are applicable to it (for example, acting as legal manufacturer, developer of specifications, contract manufacturer, component supplier, importer, logistics provider, distributor, authorized representative) and the expansion of the requirement on maintenance of the QMS to include maintaining in accordance with regulatory requirements.

A new requirement has been added to state that the organization has to establish, implement and maintain any requirement, procedure, activity or arrangement that has to be documented in accordance with the standard or applicable regulatory requirements. This not only confirms that all the documented processes have to be put into effect and kept up-to-date but also allows later clauses to simply refer to aspects being 'documented' without repeating 'established, implemented, documented and maintained' on each occasion. There is also an additional general requirement for the organization to keep records to demonstrate compliance with the requirements of the standard and applicable regulatory requirements.

The next major change is the introduction of risk-based thinking into the structure of the QMS by applying a risk-based approach to controlling the processes of the QMS. This extends the requirement in the previous edition of the standard to determine the needs for risk management throughout product realization to consideration of risk in all QMS processes. It should be noted that the wording does not require risk management as described in ISO 14971 and that, as previously mentioned, the application of risk applies to risk to the safety and performance of the medical device or meeting regulatory requirements.

New text has been included regarding management of changes to the QMS (Subclause 4.1.4). Such changes have to be evaluated for their effect both on the QMS and the medical devices that fall under that QMS, and changes to the QMS have to be managed in accordance with the requirements of the standard and applicable regulatory requirements.

The requirement concerning outsourcing (Subclause 4.1.5) has been expanded to emphasize that the organization retains responsibility for activities that it outsources, that these activities need to be controlled under the requirements for purchasing (Subclause 7.4), proportionate to the risks associated with the outsourced activities, and that these controls include written quality agreements.

5. GHTF/SG1/N055. 2009, *Definition Terms — Manufacturer — Authorized representative — Distributor and Importer* http://www.imdrf.org/documents/doc-ghtf-sg1.asp

   GHTF/SG5/N4. 2010, *Post-Market Clinical Follow-Up Studies* http://www.imdrf.org/documents/doc-ghtf-sg5.asp

   GHTF/SG1/N70. 2011, *Label and Instructions for Use for Medical Devices* http://www.imdrf.org/documents/doc-ghtf-sg1.asp

   [GHTF/SG1/N071. 2012, *Definition of Terms Medical Device and In Vitro Diagnostic Medical Device* http://www.imdrf.org/documents/doc-ghtf-sg1.asp

The final change in the general requirements for the QMS, relates to a specific requirement to validate the application of computer software used in the QMS (Subclause 4.1.6). While there were requirements in the previous edition of the standard in relation to software validation for product (embedded software or where the product was software) through the requirements for verification and validation in design and development, and specific requirements for validation of software used for production and for monitoring and measurement, there was no explicit requirement for validation of other software used in the QMS, even though validation of such software was an expectation of regulatory authorities. Such a requirement could apply, for example, to elements of Enterprise Resource Planning (ERP) software, software used for document control, and software used in managing corrective actions or preventive actions, internal and external audit activities, or calibration of instrumentation. The wording related to the validation of the computer software has been aligned to be consistent wherever it appears in the standard for different applications of software.

In relation to the documentation requirements (Subclause 4.2), including requirements for records, the following changes have been incorporated:

- The qualification that documents of external origin that need to be controlled are those that are necessary for the planning or operation of the QMS.
- Explicit statement that document controls are designed to prevent loss or deterioration of documents and that record management addresses integrity and security of records.
- Explicit requirement for changes made to records to be identifiable.

A new documentation requirement has been added in relation to protection of confidential health information. The prior edition of ISO 13485 mentioned confidential health information as part of a note as an example of customer property that had to be managed. Recognizing the increasing potential for such information to be received during complaint investigation or post-market surveillance, or contained in software returned for investigation or maintenance, together with increasing regulatory requirements for privacy, a new requirement has been added on protecting confidential health information in accordance with regulatory requirements.

The requirement on the medical device file has been placed into a separate subclause (4.2.3) and expanded to contain more detail on its content.

5. Management responsibility (MODIFIED)

The biggest changes in regard to Management Responsibility relate to management review, but prior to that subclause, there are additions to reflect management responsibility to ensure awareness of, and compliance with, applicable regulatory requirements. This is consistent with the added emphasis on regulatory requirements throughout the standard.

A documented procedure for management review (Subclause 5.6) is now required. The list of management review inputs has been expanded explicitly to include information from complaints and on reporting to regulatory authorities. The outputs now include explicit reference to changes needed to maintain the suitability and adequacy, as well as the effectiveness, of the QMS as well as references to considerations of changes in the QMS needed as a result of changes in applicable regulatory requirements.

6. Resource management (MODIFIED)

Clause 6 on resource management covers human resources, infrastructure and the work environment.

For human resources (Subclause 6.2), the new edition requires a documented procedure for the process used to establish competence, provide training and ensure personnel are aware of the importance of their activities and how they contribute to meeting the organizations objectives; this was referred to in a note in the previous edition. The standard also now requires that the procedure considers how to both achieve and maintain competence of personnel. While evaluation of the effectiveness of the actions taken to achieve competence was required in the previous edition

of the standard, a new note has been added in this revision indicating that the method selected to evaluate such effectiveness can be related to the risk associated with the activities involved. Hence for relatively simple, low risk tasks, the method of evaluating effectiveness might be quite straightforward, such as a signature indicating that the procedure has been read and understood, but for more high risk activities, the method of evaluation would need to be more sophisticated, including some aspect of testing understanding or performance.

The requirements on infrastructure (Subclause 6.3) now have to be documented and, as well as supporting achievement of conformity to product requirements, these requirements have to address orderly handling and prevention of mix-ups. The requirement on maintenance has been expanded to provide explicit reference to equipment requiring maintenance including equipment used for: i) production; ii) control of the work environment; and, iii) monitoring and measurement.

The new edition indicates that the requirements for the work environment (Subclause 6.4) have to be documented. An additional subclause has been added in relation to sterile medical devices further to expand this by requiring that the requirements for contamination control for particles and microorganisms are documented and that the required cleanliness of product is maintained during assembly or packaging.

7. Product realization (MODIFIED)

The clause on Product Realization shows the greatest impact of the renumbering of subclauses to reduce the number of four and five digit numbers, with extensive revision of the subclause numbers, but not the order of the subclauses, particularly from Subclause 7.5 onwards. In some cases, the subclause has been renumbered without any substantive change in the content.

Product realization starts with planning. A number of explicit references in the planning process (Subclause 7.1) have been added with reference to planning for infrastructure and work environment needs, traceability, handling and storage. A new requirement has been added for the output of planning activities to be documented. Finally, and most significantly in planning, the requirement on application of risk management in product realization has been modified, from establishing requirements for risk management throughout product realization in the previous edition to documenting one or more processes for risk management in product realization in the new edition. This makes explicit the need for risk management procedures to be integrated in the QMS processes in product realization.

Customer-related processes (Subclause 7.2) include determination of requirements from the customer and for the product as well as communication with customers and regulatory authorities. There is a new, explicit requirement for the organization to identify user training needs to ensure safe use of the medical device, followed subsequently by a new requirement that any training so identified is either available or planned to be available when the product is placed on the market. There is also an explicit requirement that regulatory requirements for the product are met, reflecting the additional focus on the link with regulatory requirements in the new edition. In connection with communication, there is a new requirement for communication with regulatory authorities in accordance with regulatory requirements. This has been added to this subclause to recognize that regulatory authorities can be considered customers of the organization in that they received intended outputs of the organization's processes for regulatory compliance.

There are a number of significant modifications in relation to design and development (Subclause 7.3). In particular:

- design and development planning has to address the transfer from design and development into production, as well as ensuring traceability of design inputs to design outputs and the availability of resources, including personnel competence, needed for the design and development project;
- design and development inputs need to include explicit usability requirements, and address standards as well as regulatory requirements. The inclusion of these elements as design and development inputs means that they need to be addressed in the design and development outputs and subject to review, verification and validation as appropriate;
- specific detail has been added in the records of design and development review to ensure traceability between the review and the product under development;

- the subclauses for each of design and development verification and validation have been constructed in a parallel manner with i) explicit reference to arrangements being planned and documented, ii) verification of interfaces or connections with other products when two or more medical devices are intended to be used together, and iii) additional requirements on records;
- more detail is included on the nature of the product used in validation so that it is representative and that the rationale for the choice of product used is recorded;
- in addition to the new requirement to plan design and development transfer, a new clause with explicit requirements on transfer activities has been added including requirements for procedures for, and records of, transfer from design and development to production;
- additional detail has been added on design and development changes with requirements for documented procedures for changes and linkage of the review of the change with the risk management process; and
- explicit reference to design and development records in a file of the history of the design and development activities.

The next subclause of product realization addresses purchasing (Subclause 7.4). This subclause has been extensively updated and reformatted to reflect the regulatory focus on control of suppliers. The section on the purchasing process (Subclause 7.4.1) has added requirements on the criteria to be used in a risk-based approach to evaluating, selecting, monitoring and re-evaluating suppliers. The requirements have been reordered to better reflect this sequence of activities in supplier control. The requirements on purchasing information have added detail, including written agreements that suppliers inform the organization of changes in the purchased product. This theme is picked up in the verification of purchased product, where a new requirement addresses the need for the organization to address the effect of changes identified in purchased product, whether or not they have been informed of the change by the supplier.

In the control of product and service provision (Subclause 7.5.1), the list of potential production controls has been extensively revised and reformatted: i) reference to information on the characteristics of the product, documented procedures and the like have been removed from the list as they are covered in the new Subclause 4.2.3 on the medical device file; ii) requirements on availability and use of monitoring and measurement equipment, previously two separate points in the list, have been combined; and, iii) a new requirement on qualification of infrastructure has been added.

The subclause on cleanliness of product (Subclause 7.5.2) has been extended with an additional example of 'product that cannot be cleaned prior to sterilization or its use and its cleanliness is of significance in use' being added to the list of situations requiring the organization to document requirements for cleanliness of product or contamination control.

A change in terminology has been introduced in the requirements for installation activities (Subclause 7.5.3). The term 'authorized agent', used in the previous edition, has been changed to 'supplier' to avoid confusion with the use of defined term 'authorized representative' in the new edition and to reflect the intention that, if an organization uses an external provider for its installation activities, that external party is a supplier that needs to be subject to the purchasing controls in Subclause 7.4. In regards to servicing (Subclause 7.5.4), an additional requirement that servicing records are analysed as a potential source of complaint information has been added to reflect this regulatory expectation. Additionally, the same change in terminology from 'authorized agent' to 'supplier' has been made as in the subclause on installation, for the same reasons, and an explicit link from servicing to the requirements on analysis of data, correction, corrective action and preventive action requirements in Clause 8 has been added.

The particular requirement on records of sterilization processes for sterile medical devices is unchanged.

Process validation is now covered in Subclause 7.5.6. A number of changes have been introduced including:

- a requirement for validation where a process is not verified, because the organization chooses not to perform verification rather that verification not being possible, to complement the previous criteria of processes not able to be verified;
- a new requirement to identify criteria that would trigger revalidation;
- additional text covering the use of statistical techniques in validation and the rationale for the selection of sample sizes;

- extension of the requirements on records of validation to include actions arising from validation, such as actions when predefined criteria are not met to provide traceability from validation reports to changes in processes and equipment; and
- alignment of the text on validation of software for production and service provision with the requirements on software validation for QMS software and measuring and monitoring software.

The particular requirement on validation of sterilization processes has been extended to include validation of the processes to form the sterile barrier system, recognizing that a major cause of recalls related to sterility are related to failures to maintain the integrity of the sterile barrier.

The subclauses on identification and traceability (Subclauses 7.5.8 and 7.5.9) have been reorganized, with the inclusion of the requirements from the previous subclause on status identification relocated with the other text on identification, but the requirements are not substantially changed.

New requirements have been included for preservation of product (Subclause 7.5.11). The requirements now cover preservation by use of packaging and shipping methods and, when necessary, control of the conditions during storage and transport. When special conditions, such as temperature control, are required during storage or transport, these conditions have to be controlled, monitored and recorded.

Finally, in product realization, in the control of monitoring and measuring equipment (Subclause 7.6), the only change is to align the requirements on validation of software used in monitoring and measuring with the parallel clauses for software used in the QMS and in production and service provision.

8. Measurement, analysis and improvement (MODIFIED)

The final clause of the standard addresses measurement, analysis and improvement.

The requirements for feedback (Subclause 8.2.1) now explicitly require that methods for obtaining and using feedback be documented and linked to the risk management processes for the medical device, as well has the previous requirements to link with corrective action and preventive action. A new subclause on complaint handling (Subclause 8.2.2) has been added with significant detail based on experience of regulatory expectations and the focus of regulatory authorities on this activity; this detail includes explicit requirements for documented procedures, timely complaint investigation and compliance with regulatory requirements. In addition, a new subclause on reporting to regulatory authorities has been created (Subclause 8.2.3).

In the subclause on internal audit (Subclause 8.2.4), regulatory requirements have been added as an audit criterion alongside the requirements of ISO 13485 and the requirements established by the organization in its QMS. This is consistent with the increased emphasis on regulatory requirements throughout the revision of the standard.

The subclause on control of nonconforming product (Subclause 8.3) has been restructured with the creation of a general subclause followed by separate sections on nonconformities identified before and after delivery, and rework. The new subclause on nonconformity detected after delivery now includes the requirement for a documented procedure for issue of advisory notices, which has been relocated from the general text on improvement in the previous edition of ISO 13485; this is a more appropriate location for this requirement. The requirements have been edited for consistency and to fit into the new structure but are essential unchanged.

Analysis of data (Subclause 8.4) has been amended to include:

- additional requirements that the procedures for analysis of data include the methods to be used for analysis, including statistical techniques where these are to be applied:
- more general reference to analysis of data on opportunities for improvement and not only opportunities for preventive action;
- additional requirements to include data from audits and service reports in the analysis of data; and
- links to the requirements for improvement if the analysis of data indicates that the QMS is not suitable, adequate or effective.

The general subclause on improvement (Subclause 8.5.1) has been modified by the relocation of paragraphs in the previous edition on issue of advisory notices, customer complaint records and notification of adverse events to more appropriate places in the standard. The general requirement has been strengthened by adding the focus on improvement of medical device safety and performance, as well as the suitability and effectiveness of the QMS, together with consequential reference to the use of post-market surveillance as a driver for improvement.

The requirements for corrective action (Subclause 8.5.2) have been modified by explicit requirements to reflect regulatory expectations that corrective actions are:

- taken without undue delay, in parallel to the requirement that actions from internal audit observations are taken without undue delay that was in the 2003 edition and is maintained in this edition;
- planned and documented; and
- verified to show that the action does not have an adverse effect.

Similar, parallel changes in regards to preventive action (Subclause 8.5.3) have been included in regards to planning, documentation and verification that the action does not have an adverse effect, but the requirement for action to be taken without undue delay has not been added in relation to preventive action. This is because, in regards to preventive action, no nonconformity has yet occurred whereas for corrective action there is a nonconformity that needs to be addressed.

Annex A – Comparison of content between ISO 13485:2003 and ISO 13485:2016 (NEW)

This annex has been added to summarize the changes made between the second and third editions of the standard.

Annex B – Correspondence between ISO 13485:2016 and ISO 9001:2015 (NEW)

This annex has been added to cross reference between ISO 9001:2015 and ISO 13485:2016 to assist organizations that want to be certified to both standards. Two tables are provided: one correlates the clauses and subclauses from ISO 9001 to ISO 13485 and the other correlates from ISO 13485 to ISO 9001.

Annexes Z – Relationship between this European Standard and the Conformity Assessment Requirements of EU Directives (MODIFIED)

The annexes ZA, ZB and ZC in the European adoption of ISO 13485, providing the relationship between the requirements of the conformity assessment annexes respectively of the AIMD 90/385/EEC (as amended), the MDD 93/42/EEC (as amended) and the IVDD 98/79/EC, have been updated to reflect the new content of the standard. The annexes have been enhanced to indicate some additions to the organization's QMS necessary to meet the European regulatory requirements when the regulatory requirements are partially covered by the requirements in EN ISO 13485:2016. In addition, the annexes have been reformatted in accordance with the latest template for the annexes Z agreed between CEN and the European Commission Services.

Reviewers
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