Avoiding Surprises When Implementing a Single Quality System

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European medical device manufacturers are sometimes surprised to learn that operating ISO 13485 alone is not sufficient to meet United States (US) quality system requirements. This article discusses important considerations for meeting US and European requirements when operating under a single quality system.

Important similarities
The United States (US) Quality System Regulation (QSR) (21 CFR 820) is based on the Committee Draft version of ISO 13485:1996, Quality Systems, Medical Devices, Particular Requirements for the Application of ISO 9001. ISO 13485:1996 included specific requirements for medical device quality systems and had to be used with ISO 9001:1994. The quality system structure described in those standards was based on 20 distinct quality system elements. The US QSR is also largely based on those 20 quality system elements, but it includes additional provisions.

ISO 13485 was then revised to be a standalone standard that contains the medical device requirements and ISO 9001:2000 provisions in one standard. However, the revised standard was no longer based on distinct quality system elements, but on the process approach on which ISO 9001:2000 is based. The “process approach” is considered to be the application of a system of processes within an organisation, together with the identification and interactions of those processes and their management. In spite of this difference, the QSR has much in common with ISO 13485:2003. This is because every effort was made by the developers of the revised version of ISO 13485 to maintain the level of quality system requirement for medical devices that had already been established. Thus, although the structure of the quality system described in ISO 13485:2003 differs from that described in the QSR, many of their requirements are similar. However, important differences exist, therefore, it is critical that companies understand that conformity with ISO 13485 alone will not fully satisfy US quality system requirements.

Differences in requirements
A discussion of all differences between ISO 13485:2003 and the QSR is beyond the scope of this article. Readers are encouraged to have an understanding of all differences that could lead to noncompliance with the QSR if merely the clauses of ISO 13485 are implemented.

Signatures. The QSR contains a number of provisions that require the signature and date of an individual, for example, the individual approving documents and document changes, design input requirements and the design output. ISO 13485 specifies that documents and document changes, design input requirements and the design output be approved, but there is no specification that the approval should include a signature and date. Therefore, companies that conform only to ISO 13485 sometimes fail to comply with the QSR requirement.

Change procedures. The US Food and Drug Administration (FDA) places considerable emphasis on the control of production and process changes. Manufacturers are required to establish and maintain procedures for changes to a specification, method, process or procedure. This includes changes to inprocess test methods or production equipment or test instruments. These changes must be
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steps to ensure compliance with each provision of the QSR.

requirement is often not met by companies that operate under
for a production work order, supplier evaluation and surveil-
lation, the management of materials and components needed
incoming goods, the release of incoming goods to produc-
the quality system. This means that computer systems used
used as part of production, but also if they are used as part of
the quality system. This means that computer systems used
for controlling activities such as the identity and release of
incoming goods, the release of incoming goods to produc-
tion, the management of materials and components needed
for a production work order, supplier evaluation and surveil-
ance information and other activities must be validated.
This requirement is often not met by companies that operate under
a quality system certified to ISO 13485 and have not taken
steps to ensure compliance with each provision of the QSR.

Differences in interpretation
In some instances, the requirements of ISO 13485 and
the QSR are virtually identical, but how FDA interprets the
correct compliance to a requirement can be significantly
different from how ISO 13485 auditors do.

Process validation. Both ISO 13485 and the QSR have
similar requirements for process validation. ISO 13485
requires the validation of any processes for production
and service provision where the resulting output cannot
be verified by subsequent monitoring or measurement.
This includes any processes where deficiencies become
apparent only after the product is in use or the service
has been delivered. The QSR requires the validation of
processes where the results of the process cannot be fully
verified by subsequent inspection and test.

Companies that have not checked or do not have
knowledge of FDA process validation expectations are
often surprised to learn that they have not validated all
processes that FDA believes should be validated, and/or
their validation documentation is found to be inadequate
to demonstrate validation with a high degree of assurance
as required by the QSR. When this occurs, it may mean
that significant resources and expertise are needed to
correct the process validation deficiency.

Examples of other requirements where FDA may inter-
pret the adequacy of compliance in a different manner
from a quality system auditor include software validation, the
control of design changes, the management of complaints,
and management of corrective and preventive actions.

Single quality system structure
Medical device companies generally find that the most sensi-
tible means of complying with US and European quality system
requirements is to establish a single quality system that com-
plies with both the QSR and ISO 13485. A common method
for implementing this type of system is to develop a matrix
or map of corresponding requirements and procedures. For
example, a company that operates under an ISO 13485 qual-
ity system, but needs to also comply with the QSR, can after
establishment of the first system develop a matrix that lists
the quality system processes and corresponding sections of
the QSR. The addition of procedures and in some cases work
instructions to this matrix increases its utility in demonstrat-
ing compliance with both sets of requirements.

Developing a matrix is not the only measure that should
be taken. Many medical device companies fail to include the
provisions of the QSR in their internal audit programmes.
Audits are frequently conducted to evaluate the requirements
of ISO 13485 and not of the QSR even if the company has
been marketing in the US for years. Companies that do this
are incurring a significant risk. If FDA determines, most
commonly through a facility inspection, that important QSR
requirements are not being met, costly enforcement actions
may be taken, which are discussed below.

Another approach that companies are advised to take,
which can increase the effectiveness of their internal
audits, is to include a review of the ISO 13485 and QSR
quality system requirement before proceeding with the
audit. However, companies that have been operating for some
time under a quality system tend to evaluate only whether
or not company standard operating procedures (SOPs) and
work instructions are being properly followed; this may not
be sufficient to ensure an effective audit. This is because there
are instances when SOPs or work instructions fail to meet the
basic requirements of ISO 13485 or the QSR. In some cases,
options regarding what may be an adequate procedure or
work instruction to fulfil a particular requirement may have
changed because of increased awareness or knowledge of
the requirement. Thus, the underlying requirement as well
as compliance with SOPs and work instructions should be
checked during internal audits. Important compliance prob-
lems can be resolved or even avoided using this technique.

Consequences of noncompliance
With few exceptions, the QSR applies to medical devices
marketed in the US. It is a regulation, in contrast with ISO
13485, which is a voluntary standard evaluated by means of
a quality system audit by a European Notified Body. When
nonconformities are identified by a Notified Body during a
quality system audit, a list of nonconformities is provided to
the company being audited. In some cases, the company is
requested to provide a written corrective action plan, but in
many cases the corrective actions are checked during the next
audit. If the nonconformities are serious, withdrawal of the
quality system certificate is possible. There is no public infor-
mation on how often this occurs, but indications are that it is
relatively uncommon.
In contrast, failure to comply with the QSR can lead to the medical device being considered adulterated and/or misbranded and subject to various enforcement actions depending on the seriousness of the violation. FDA investigators document noncompliance with the QSR on a form 483 that is provided to the company at the end of a facility inspection and the company is given a specified time to respond to the inspection findings. For manufacturers located outside the US, serious violations may lead to a Warning Letter and possibly a refusal to allow the device to be imported into the US. This can have devastating effects on a medical device company and is an important reason why companies need to ensure that they fully comply with US quality system requirements.

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