UNANNOUNCED EU MEDICAL DEVICE AUDITS BY NOTIFIED BODIES: IMPACT ON SUPPLIERS

Executive Summary

European Medicines Agency (EMA) regulations for licensing of medical devices include the use of authorized and accredited organizations, known as Notified Bodies, for evaluating manufacturers and verifying conformance to quality standards. Notified Bodies are required to conduct regular audits to verify the manufacturer's conformance and periodically must include audits that are unannounced.

Based upon the application filed by a medical device manufacturer, a Notified Body may identify certain suppliers as critical to conformance of the device. Suppliers identified as critical are subject to audits, both announced and unannounced, as part of the device manufacturer's license approval or as part of ongoing surveillance.

EU medical device regulations are clear that suppliers identified as critical to a device may also be subject to audits from Notified Bodies, including unannounced audits. Failure to comply with a Notified Body audit may jeopardize the device manufacturer's application and/or license and may lead to negative consequences for the business relationship between manufacturer and supplier.

Scope

This discussion applies to medical device and components regulated by the European Union, and focuses on Notified Body audits relating to suppliers to medical device manufacturers, such as West. In this context, medical device manufacturers are customers to whom West provides products or services for those devices.

Glossary of Terms

Critical Subcontractor:	Subcontractors in charge of processes which are essential for ensuring compliance with legal requirements
Crucial Supplier:	Supplier of crucial components or of the entire devices
EU:	European Union
EMA:	European Medicines Agency
Member State:	Constituent sovereign nations comprising the European Union
Notified Body:	An entity accredited by an EU Member State to assess medical devices intended for the EU market for conformance to established standards.

Background

The EU maintains regulations for different types of medical devices[1][2][3]. These regulations include the use of Notified Bodies, which are independent non-governmental organizations accredited to evaluate devices for conformance to applicable standards and regulations.

Each Member State in the EU may accredit Notified Bodies. The EU maintains a list of these organizations, assigns an identification number to each, and maintains requirements for their control and evaluation. The applicant will choose a Notified Body from the existing list of accredited organizations[4] and send their application to them. The selected Notified Body will perform an assessment and, pending a successful outcome, will issue a certification known as a CE mark.

Manufacturer Audits

In addition to licensing audits, EU regulations include guidelines for ongoing surveillance of device manufacturers to demonstrate that they maintain conformance with their approved quality system. During an audit, the Notified Body has the right to request that tests be performed in order to verify that the manufacturer's quality system is functioning as intended. The regulations also permit these audits to be conducted unannounced.

The Notified Body is responsible for conducting periodic surveillance audits on the manufacturer and for providing them with an assessment report afterward. Notified Bodies are required to share relevant information from quality systems audits with other Notified Bodies, when requested.

The device manufacturer is also required to inform the Notified Body that conducted the quality system audit of any planned changes to that system. A review is performed to determine whether the changes will still meet established requirements for the product. The device manufacturer is required by regulation to allow the Notified Body access to relevant facilities and supporting information.

Application to Device Manufacturer Suppliers

Audits conducted by Notified Bodies are required to be performed at the device manufacturer's facility and, when substantiated, on the premises of the manufacturer's suppliers.

The EC has issued more detailed guidelines pertaining to Notified Body audits[5], which elaborate and expand the scope beyond the device manufacturer to say:

---

[1] Active Implantable Medical Device Directive (90/385/EEC)
[2] Medical Device Directive (93/42/EEC)
[3] In Vitro Diagnostic Medical Device Directive (98/79/EC)
[4] New Approach Notified and Designated Organisations (NANDO) at: http://ec.europa.eu/growth/tools-databases/nando/
[5] Commission Recommendations on the audits and assessments performed by Notified Bodies in the field of medical devices (2013/473/EU)

> …if this is likely to ensure more efficient control, one of its subcontractors in charge of processes which are essential for ensuring compliance with legal requirements *(*'critical subcontractor') ***or a supplier of critical components*** or of the entire devices (both: 'crucial supplier') without prior notice ('unannounced audits')…

Review of different guidelines on this subject indicate that the terms "critical" and crucial" are used interchangeably. For the purposes of this paper, the term "critical" will be used.

This guideline states that Notified Bodies should refrain from signing agreements with manufacturers unless:

> …they receive access to **all critical subcontractors and crucial suppliers** and thus **to all sites where the devices or its crucial components are produced,** regardless of the length of the contractual chain between the manufacturer and the subcontractor or supplier

Guidelines for Notified Body audits make it clear that the device manufacturer is ultimately responsible for exercising control of their suppliers and subcontractors. The device manufacturer must demonstrate in their application the type and extent of control that is applied to third parties that carry out design, manufacture, inspection and testing or the product, or elements thereof. Adequate control is not necessarily demonstrated by merely referencing a supplier's technical documents.

Defining Critical Suppliers

A **critical supplier** for medical devices is defined[6] in the EU as:

> A supplier delivering materials, components, or services that may influence the safety or performance of the device

In the context of a Notified Body audit, a **critical supplier** is:

> A supplier of a product or service, the failure of which to meet specified requirements could cause unreasonable risk to the patient, clinician or others, or could cause a significant degradation in performance.
>
> This can include suppliers of services, which are needed for compliance with QMS or regulatory requirements, e.g. internal audit contractors or Authorized Representatives

The determination of which suppliers are critical is made by the Notified Body. This determination should be risk-based and the decision process should be documented. Identification of critical suppliers is made based on the technical file submitted by the device

[6] Guidance for Notified Bodies auditing suppliers to medical device manufacturers (Notified Body Operations Group, NBOG BPG 2010-1)

manufacturer to support their license. The manufacturer should provide a risk assessment and to determine which items are critical. If a Notified Body determines that a supplier is critical, they must notify that supplier in advance of that designation.

Designation as a critical supplier does not automatically require that the supplier is subject to requirements in EU medical device regulations. However, this designation does mean that the supplier is subject to Notified Body audits, both scheduled and unannounced.

Critical supplier products or processes may include:

- Finished products
- Primary packaging
- Sterilization
- Contract laboratory testing for biocompatibility
- Design, distribution, regulatory compliance services
- Labeling
- Previous cases where conformity was influenced by supplier activities and where the manufacturer fails to demonstrate sufficient supplier control.

Audits may also be triggered by post-market information such as:

- Field Safety Corrective actions impacting on the supplier's processes or products
- Complaints relating to the supplier's processes or products
- Post-market information (e.g. clinical investigations, public information, etc.) relating to the supplier's processes or products

If the device manufacturer fails to provide adequate assurance of control of their critical suppliers, the Notified Body must audit those suppliers. Notified Bodies may audit critical suppliers in addition to, or instead of, the device manufacturer.

Unannounced Audits

Unannounced audits of a device manufacturer should take place at least once every three years; the frequency should be increased in higher risk cases, for example:

- High risk medical devices
- Devices of the type are frequently non-compliant
- Cases where information exists that gives reason to suspect non-conformities may exist

Timing of unannounced audits should be unpredictable. Audits should assess the effectiveness of the device manufacturer's control of the supplier, and the supplier's ability to consistently meet the manufacturer's requirements.

The Notified Body will compile an audit report that will be sent to the device manufacturer and will note any non-conformities identified. In the case of a supplier audit, it is the device manufacturer's responsibility to discuss these findings with the supplier.

The contract between a device manufacturer and a Notified Body should cover the issue of access to manufacturing facilities, and it should also include access to the facilities of critical suppliers. Guidelines also recommend that contracts between device manufacturers and suppliers include provision for access to the supplier's premises by the manufacturer, Notified Body and Competent Authority. Contractual agreements should also authorize Notified Bodies to terminate a contract with a device manufacturer that no longer assures access to facilities.

As a best practice, identified critical suppliers should be informed of the need to provide access and their consent should be requested.

Suppliers should comply with unannounced Notified Body audits since failure to do so could jeopardize the device manufacturer's contract with the Notified Body and, consequently, their CE certification.

Recommendations

As a supplier of device components, West should be informed when their status is deemed to be critical and consent should be requested regarding access to West facilities for Notified Body audits. In cases where status is unclear, it is recommended that West contact the device manufacturer to confirm whether it has been identified as a critical supplier for that manufacturer's device.

In cases where West has been identified as a critical supplier to a device manufacturer in the EU, applicable West facilities should be prepared for the possibility of a Notified Body audit. Should an audit occur, the West facility should be prepared to comply, regardless of whether the audit was previously announced or not.

Results of a Notified Body audit should only be shared with the device manufacturer. Failure of a supplier to comply with a Notified Body audit would be communicated to the manufacturer. Ultimately, it would be the device manufacturer's responsibility to decide whether to maintain their relationship with a given supplier. However, actions taken by a supplier that put a manufacturer's compliance status in jeopardy could be expected to have negative consequences to their relationship.

Steve LoCastro
Director, Regulatory Affairs
West Pharmaceutical Services, Inc.