Top Ten CE Marking Issues

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“Experience is the name everyone gives to their mistakes”
-- Oscar Wilde
Learning Objectives

• Understand the value of being properly prepared when engaging with an EU Notified Body.

• Realize how correctly classifying a medical device impacts its route to conformity.

• Verify the status of subcontractors working in your supply chain.

• Be aware of the requirement for appropriate Post Market Surveillance.

• Considerations for an efficient approval of products that require third party input - Medicinal CA’s and Member States; for NB certification decision.

• Effective use of harmonized standards.

• Document control considerations.
Issue #1

- Assuming that regulatory clearance in the US is a gateway to CE Marking in Europe

You’ll take our FDA approval into account, right?
Can we use all the same data?
#1 Assuming Regulatory clearance in US is gateway to CE Marking in Europe

Situation

• Unlike FDA, multiple institutions share the responsibility for regulatory approval and monitoring in Europe: Member states, Competent Authorities, and Notified Bodies.

Implication

• Previous FDA regulatory clearance plays no part in the certification decision. In order to place the CE Mark on your product, it must meet the ERs of the appropriate Directive. No mutual recognition; no “rubber stamp”.
#1 Assuming Regulatory clearance in US is gateway to CE Marking in Europe

**Resolution**

- Medical devices in the EU are governed by one of three Medical Device Directives (MDD, AIMD, IVDD) and other Directives may apply as well depending upon your technology. It is against these, that all certifications are judged.

- Going through the process of getting clearance by FDA won’t hurt and should help in your ability to present your technical file or design dossier to the NB for review.

- Significant guidance (MEDDEVs, NB-MEDs, GHTF, EN / ISO Standards, etc.) is available to help interpret the meaning of the Directives.
Issue #2

- Your Product does not fit the definition of a medical device in the EU

*Do we have to market this as a medical device?*

*What classification is this product in Europe?*
#2 Product does not fit definition of medical device in Europe

**Situation**
- You have created a new product that consumers will quickly embrace but it is actually a cosmetic or drug or personal protective equipment or food or lab equipment (or something else) but it is not a medical device as defined by one of the Directives.

**Implication**
- You have wasted time, effort, and money believing (or assuming) that your product can be CE marked under the MDD when it cannot.
#2 Product does not fit definition of medical device in Europe

Resolution

• Some devices are primarily cosmetic but have some medical device uses. Unfortunately, many times we see the dossier (particularly risk / CER / PMS plan) focused on cosmetic use.

• It may be possible for such products to be CE marked under the MDD but focus should be on medical use. This is very different from US so this often causes problems.

• EU regulations require demonstration that the medical device is safe AND performs as intended. Cosmetic devices in the US do not require demonstration of performance. Only safety issues are considered for Medical Device Reports (vigilance reports for significant device adverse events).
#2 Product does not fit definition of medical device in Europe

**Resources**

- Classification of EU devices is generally based on the device risk level and considers where and how long they are used. Be aware that a single product could fall under multiple Directives. One point often missed is that if several rules apply to the device, the strictest rules resulting in the higher classification prevail.

- Guidance: [MEDDEV 2.4/1 Rev 9 (June 2010)](#)
Issue #3

- Your Subcontractors do not possess appropriate quality certification for the work they perform for you

  *We’re not sure what certificates our contractors have. We don’t do any of the actual work, is that OK?*
#3 Subcontractors do not possess appropriate quality certification

Situation

Your NB has asked for copies of QMS certificates held by your significant subcontractors and one or more of the following is true. Subcontractor has:

- No QMS certificate.
- An expired QMS certificate.
- A valid QMS certificate but its scope does include the product or service provided to the manufacturer.
- A valid QMS with an appropriate scope but was not issued by an EU/EEA Notified Body.
- A valid QMS but issued for an address other than the location used / specified by the manufacturer.
#3 Subcontractors do not possess appropriate quality certification

**Implication**

- The accreditation, location, and scope of a Subcontractor quality system certificate are very important and should be considered carefully.
#3 Subcontractors do not possess appropriate quality certification

Resolution

• Many legal manufacturers purchase aspects of the device technology or utilize subcontractors for significant portions of the design, testing, or manufacturing.

• Since the legal manufacturer is ultimately responsible for the device being placed on the market, it is critical that sufficient detail about the subcontractor’s work is known in order to address the Essential Requirements.

• Regardless of whether the contributing party has obtained regulatory clearance, it is still the responsibility of the legal manufacturer to ensure compliance with the MDD.
#3 Subcontractors do not possess appropriate quality certification

**Resolution**

- If a significant subcontractor does not hold an ISO 13485 Certificate from an EU/EEA NB* (or an affiliate organization that is also a NB), then an audit of that subcontractor may be required prior to issue of an EU Quality Assurance Certificate (Annex II – Annex VI certification). An ISO 9001 Certificate will not be satisfactory.

  *NB’s will accept CE or GMP license for medicinal substance activity.

- Notified Body practices may vary so the legal manufacturer should discuss this with their NB ahead of seeking certification.

**Guidance:**

- Manufacturer can verify if the organization that issued the ISO 13485 certificate is a Notified Body (or affiliate) by reviewing the following website: [http://ec.europa.eu/enterprise/newapproach/nando](http://ec.europa.eu/enterprise/newapproach/nando)
Issue #4

- Lack of risk appropriate Clinical Evaluation Report

  I can give you a ton of hits on PubMed, is that enough?
  This is just a summary of the literature, right?
  What’s a clinical evaluation report?
#4 Lack of risk appropriate Clinical Evaluation Report

**Situation**

- You weren’t aware that regardless of device classification, conformity with the ERs must include a risk appropriate Clinical Evaluation Report (CER) on the subject device or equivalent devices that is conducted by individual(s) with appropriate qualifications to evaluate the technology, research methodology, and clinical diagnosis / management. For implantable and EU Class III devices, a clinical investigation is also required unless duly justified to rely on existing clinical data.
#4 Lack of risk appropriate Clinical Evaluation Report

Implication

• Some manufacturers mistakenly interpret this requirement to mean that only a literature review and predicate device substantial equivalence (similar to what is required in a US 510[k]) must be demonstrated.

• Many people think that if they get their device CE marked based on a CER with literature of comparative devices (with no clinical trial), that they don’t have to do PMCF on their device. This is likely to be wrong.
#4 Lack of risk appropriate Clinical Evaluation Report

**Resolution**

- The CER is a required element for certification, but completion is often seen only as a regulatory hurdle and left to the end of the development cycle.

- However, if postponed, there is no opportunity for the CER to influence the design of the device and certification could be delayed in order to address emerging findings from similar devices impacting clinical safety or performance.
#4 Lack of risk appropriate Clinical Evaluation Report

Resolution

• The CER is also not just an accounting of the literature for devices similar to the subject device.
• Search strategy and assessment should be representative of EU Population and state-of-art there.
• Guidance document MEDDEV 2.7/1, Rev 3 explains how equivalence should be judged in order to utilize data from other devices to support the safety and performance of the subject device.
• Justifications must be made to address differences between cited and subject devices and an analysis should be done on each of the cited references and their contribution to deciding overall safety and performance.

Resources

• Guidance MEDDEV 2.7/1, Rev 3
Issue #5

• Not having an appropriate Post Market Surveillance Plan or not executing an approved plan

  We have a PMS Procedure, that’s enough, right?
  We log every complaint, is that good enough?
  How much PMS should I be doing?
#5 Not having an appropriate Post Market Surveillance Plan or not executing an approved plan

**Situation**

- Manufacturer has a variety of devices of varying levels of risk and uses their PMS procedure as the basis of their PMS Plan.

**Implication**

- This may not be sufficient to support CE marking of a device. A PMS / PMCF Plan specific to a device / group of devices is usually needed to confirm clinical performance and safety throughout the expected lifetime.
#5 Not having an appropriate Post Market Surveillance Plan or not executing an approved plan

Resolution

• Short- or medium-term (relative to intended device lifetime) clinical data may be sufficient to justify not doing a clinical investigation but may not be sufficient to warrant not doing Post-Market Clinical Follow-up (PMCF).

• Annex X of the MDD requires that the clinical evaluation and its documentation must be actively updated with data obtained from the post-market surveillance (PMS).

• If the original PMS Plan does not provide anticipated data, manufacturer should change plan and review with the NB before the time of renewal.
#5 Not having an appropriate Post Market Surveillance Plan or not executing an approved plan

**Resolution**

- Hazards identified during PMS must also be actively compared to those identified in the risk management file, which must be updated if new hazards are identified or previous assumptions are found to be no longer valid. The linkage between risk management and PMS is fundamental to continued device certification and is frequently missed.

**Guidance:**

- **MEDDEV 2.12/ 1 Rev 8 & MEDDEV 2.12/ 2 Rev 2**
Issue #6

- Expecting a fast approval of your Device-Drug combination product

You can get this done quickly, right?
Is this thing considered a drug in Europe?
#6 Expecting a fast approval of your Device-Drug combination product

**Situation**

- You didn’t actually know the particular substance within your device is considered a drug under EU regulation. Examples include vitamins, herbs, extracts (i.e. thyme, fennel, clove oil, menthol, etc).

- You stated that a device was not considered a class III combination device because the drug component is trapped and not “liable to act” (per Annex IX, Rule 13) but no data were provided.
#6 Expecting a fast approval of your Device-Drug combination product

Implications

• In general Device-Drug combinations are ruled class III under the MDD and require both a device review by the NB as well as a medicinal consultation with a Competent Authority.

• The consultation process timeline is 210 days. The dual nature of this process is very likely to push out your timelines for product approval and release.
#6 Expecting a fast approval of your Device-Drug combination product

**Resolutions**

- Drug/device (or Biologic/device) combination products are becoming more prevalent in the healthcare sector. If a device contains a drug or biologic, a NB will request a lot of information about that medicinal substance: formulation, dosage, and performance of the drug *in situ*.

- The Competent Authority will want to assess the Quality and Safety of the drug substance and the quality of how the drug is incorporated in the device, the non-clinical data of the drug substance and the safety / usefulness of the drug in the device “risk vs benefit profile”.

- The level of the review will be impacted by whether the drug is known for the indicated use and whether the drug source is known to the CA.
#6 Expecting a fast approval of your Device-Drug combination product

**Resolutions**

- The MDD does not consider the “level” of the active ingredient. Manufacturers often say the levels are “below a therapeutic level” but what is important is its liability to act at that level.

- Where claims are made that a drug is present but “not liable to act”, the manufacturer will often need to demonstrate this through scientific data (i.e. in vitro or in vivo studies).

- If in doubt, it is recommended that you talk with the NB to help sort through classification and submission issues early in the development process.
Issue #7

• Submitting a technical file or design dossier that is poorly assembled

*Should I send an electronic copy of the Tech File?*

*Do all the documents need to be searchable?*
#7 Submitting a technical file or design dossier that is poorly assembled

(OR) Notified Body is not provided with all the information needed for completing the review.

**Situation**
- You have completed the most challenging aspects of compiling your technical file or design dossier, but it is disorganized and therefore difficult for the NB reviewer to access and evaluate.

**Implication**
- A poorly organized submission wastes time and therefore money while the reviewer struggles to get through it.
#7 Submitting a technical file or design dossier that is poorly assembled

**Resolution**

- Anticipate the needs of the technical expert who is going to review your documentation. Some items to consider include multiple vs. single files, bookmarks, inclusion of referenced documents, or electronic vs. paper copies. All referenced reports should be available for review.

**Resources**

- BSI offers a “Best Practices” set of guidelines.
- Guidance: [GHTF/ SG1/ N011:2008; NB-MED/ 2.5.1/ Rec 5](#)
Issue #8

• **Expecting a fast approval of your device that utilizes animal tissue**

**Situation**

• You didn’t actually know your device is manufactured utilizing tissues of animal origin. Examples include: Product coating or impregnation – collagen, gelatine, heparin OR used in the manufacturing process – tallow derivatives such as oleates and stearates, foetal calf serum, enzymes, culture media.

• You stated that the device was not considered as containing animal tissue per Annex IX, Rule 17, and did not provide related supporting data.
Issue #8 Expecting a fast approval of your device that utilizes animal tissue

Implications

• Animal tissue raises concern in the EU and typically more scrutiny is applied.

• Manufacturers often demonstrate the risk is minimized but EN ISO 22442-1 requires that benefits outweigh the associated risks relative to lower risk material alternatives. This can also be a problem for manufacturers already selling product in the US as this is not required. The result may be having to substantially limit the indications in EU because of this.
Issue #8 Expecting a fast approval of your device that utilizes animal tissue

**Resolutions**

- **Definition of Animal:** any vertebrate or invertebrate [including amphibian, arthropod (e.g. crustacean), bird, coral, fish, reptile, mollusc and mammal] excluding humans (Homo sapiens).

- In general devices manufactured utilizing tissues of animal origin or derivatives rendered non-viable are Class III except where such devices are intended to come into contact with intact skin only. Under the MDD & AIMD such devices require a review by the NB in addition to informing the competent authorities of the other Member States and the Commission of their assessment carried out by means of a summary evaluation report (SER).

- The competent authorities of the Member States may submit comments on the SER within the following deadlines:
  - (i) for medical devices using starting materials for which a TSE certificate of suitability has been submitted, 4 weeks and
  - (ii) for medical devices using starting materials for which a TSE certificate of suitability **has not** been submitted, 12 weeks.
Issue #8 Expecting a fast approval of your device that utilizes animal tissue

Resolutions

• Devices manufactured utilizing tissues of animal origin products are becoming more prevalent in the healthcare sector. If a device contains tissues of animal origin, a NB will request a lot of information on the animal tissue regarding: risk management, sourcing and viral inactivation.

• The member States will want to ensure safety of the animal tissue when used in humans. Additionally, that the animal tissues are used to provide performance characteristics that have advantages over lower risk animal species or non-animal based materials.

• The level of the review will be impacted by whether the animal tissue derivative is from a source “fit for human consumption” and/or if there is a TSE certificate of suitability.
Issue #8 Expecting a fast approval of your device that utilizes animal tissue

**Resolutions**

- The process of a NB assessment, submitting an SER to a coordinating CA, receiving responses from Members states through the coordinating CA and analyzing the responses is very likely to push out your timelines for product approval and release.

- If in doubt, it is recommended that you talk with the NB to help sort through classification and submission issues early in the development process.
Issue #8 Expecting a fast approval of your device that utilizes animal tissue

Resources

• 722/2012/EC EU Regulation with respect to active implantable medical devices and medical devices manufactured utilizing tissues of animal origin.
  ➢ Includes requirements for species considered to be susceptible to transmissible spongiform encephalopathies (TSE):
    o Bovine, ovine, caprine species, deer, elk, mink, and cat
    o Collagen, gelatin, and tallow must meet requirements for human consumption

• EN ISO 22442 – 1: Risk management
• EN ISO 22442 – 2: Control of Sourcing
• EN ISO 22442 – 3: Validation elimination and/or inactivation of viruses
Issue #9

• **Conformity with Harmonized Standards cannot be demonstrated**

**Situation**

• A manufacturer does not use any published standard because the work is proprietary and No standards currently exist or uses a standard that is not EU Harmonized.

• Clients can get into trouble when they don’t comply with a standard and they provide no gap analysis / justification regarding their solution.

• Each EU harmonized standard contains an informative “Annex ZA” which gives the cross-reference between clauses in the standard to the applicable ERs. Many new manufacturers aren’t aware of this.
Issue #9 Conformity with Harmonized Standards cannot be demonstrated

**Resolution**

- **Use of Standards**
  - First choice is harmonized standards
  - Then…
    - European (ENs not harmonized)
    - International (ISO/IEC)
    - EU national (BS/DIN/FN)
    - Other national (CSA/ANSI/ASTM)
    - Manufacturer’s specifications
Issue #9 Conformity with Harmonized Standards cannot be demonstrated

Resolution

• Member States presume compliance with the essential requirements in respect of devices which are in conformity with the relevant national standards adopted pursuant to the harmonized standards.

• If you don’t use harmonized standards that is fine, but you will be expected to have a solid rationale to explain your decision.

• In situations (proprietary technology areas) where there are no published standards, technical specifications or guidance documents, manufacturers’ specifications including controlled Laboratory Note books may suffice but with a sound scientifically based rationale/explanation.

Resource

• Harmonized standards are listed on the EU Commission site:
Issue #10

• Inadequate Documentation Control

The key to achieving CE marking is a successful QMS audit only? Technical documentation assessment is not really as important as QMS audit?
Issue #10 Inadequate Documentation Control

**Situation**

- During a QMS audit, non-conformities were raised due to the following/combination of findings (list is not exhaustive):
  - Incorrect version referenced either in the procedure or on the production floor.
  - Improper control of documents of external origin (e.g., Guidance).
  - Incorrectly completed change request (missing signatures & dates, incorrect signatories).
- As part of the QMS assessment, a Technical Documentation review revealed the following non-conformities/deficiencies (list is not exhaustive):
  - Not clear how documentation is controlled.
  - Technical Documentation contents not all controlled or signed/dated.
  - DOC date precedes date of Technical Documentation.
  - Signed DOC provided in DD submission.
  - Approval date, revision, signatory name / function not identified on documents.
  - Documents approved by individuals w/ insufficient credentials (particularly for Biocompatibility and CER).
  - There is No executive summary / reason for supplementary submission is not clear.
  - Insufficient detail in section summaries (to find or understand data).
Issue #10 Inadequate Documentation Control

**Implications**

- Non-conformities due to inadequate document control delay issuing of a Quality Assurance certificate.

- A technical documentation review that raises lots of non-conformities wastes time since the non-conformities must be closed out before progressing to certification stage.

- Delayed time to achieving CE Mark and being late on the EU market costs money and may lead to a lost opportunity.
Issue #10 Inadequate Documentation Control

Resolution

• The manufacturer must ensure application of the quality system approved for the design, manufacture and final inspection of the products concerned. All aspects relating to both the Quality management system - processes that lead to product realization; and verification & validation of the product must be satisfactorily addressed before a product is placed on the EU market.

• All the elements, requirements and provisions adopted by the manufacturer for their quality system must be documented in a systematic and orderly manner in the form of written policies and procedures such as quality programs, quality plans, quality manuals and quality records.

• Documents - including Technical Documentation, required by the quality management system shall be controlled. Records are a special type of document and shall be controlled via an established documented procedure.
Issue #10 Inadequate Documentation Control

Resources

• EN ISO 13485:2012
## 10 CE Marking Issues Summary

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Questions Please?