Improving Technical Documentation

Key pit falls to avoid in preparing technical documentation

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Overview

• Provide an understanding on the requirements for technical documentation

• Provide an understanding on how/what Notified Bodies assess in technical documentation reviews

• Address some key pitfalls when preparing technical documentation
Case 1: CE Marking

• The key to CE marking is passing the QMS audit
• Fact or Fiction?
Case 1: CE Marking

- The key to CE marking is passing the QMS audit
- Fact or Fiction?

- One of the biggest pitfalls...
  - Some deem technical documentation assessment not really as important as QMS audit!
  - ... an after thought?
CE Marking Process – Medical Devices

Medical Device? Classification?

Select Conformity Assessment Route

Notified Body Conformity Assessment

Sign Declaration Of Conformity, and Affix “CE Mark”
CE Marking Process – Medical Devices

1. Medical Device? Classification?
2. Select Conformity Assessment Route
3. Notified Body Conformity Assessment
4. Sign Declaration Of Conformity, and Affix “CE Mark”

- QMS
  - ISO 13485
- Technical Documentation
  - 93/42/EEC (MDD)
  - 90/385/EEC (AIMD)
CE Marking: Similar Requirements (MDD vs AIMD)

93/42/EEC (Medical Device Directive)

90/385/EEC (Active Implantable Device Directive)
Requirements: Technical Documentation

93/42/EEC, Annex VII (section 2):
• "The manufacturer must prepare the technical documentation described in Section 3..."

93/42/EEC, Annex VII (section 3):
• "The technical documentation must allow assessment of the conformity of the product with the requirements of the Directive"

• Requirements in many other Annexes and 90/385/EEC
Technical Documentation

Requirements - the Basics
Technical Documentation – 93/42/EEC

Annex VII (section 2):
• “The manufacturer must prepare the technical documentation described in Section 3…”

Annex VII (section 3):
• “The technical documentation must allow assessment of the conformity of the product with the requirements of the Directive”
Technical Documentation: NB Assessment

• NB scrutiny of documentation increases with risk classification
  • ...and novelty
Contents of Technical Documentation
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• The requirements technical documentation content stated in MDD:
  • Annex VII (explicitly)
  • Conformity assessment Annexes (Annex II, III, VI, V, VI)

• The requirements technical documentation content stated in AIMD:
  • Conformity assessment Annexes (Annex 2, 3, 4, 5)

• 93/42/EEC (MDD) ⇔ 90/385/EEC (AIMD)
Content of Technical Documentation (Annex VII)

- Product description, variants, intended use(s),
- Design drawings, manufacture process...
- Risk analysis, standards applied (full or part)
- Sterilisation method and validation reports
- Essential requirements (proof of compliance)
- Pre-clinical evaluation, design verification
- Solutions adopted for device to conform to safety principles w.r.t. state of the art
- Clinical evaluation (Annex X, includes PMS/PMCF)
- Labels and instructions for use
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Annex II (MDD)
Annex I (AIMD)

- Statement if device incorporates... “a medicinal substance or a human blood derivative” – NB assesses usefulness
- Statement on “utilisation of animal tissue”
Guidance to expand upon the Requirements
Key Guidance Documents

• NB-Med 2.5.1 Technical Documentation (2000)

• IMDRF/RPS WG/N9 (2014) - Non-In Vitro Diagnostic Device Market Authorization Table of Contents (nIVD MA ToC) Regulated Product Submissions ToC WG
  • GHTF SG1 Summary Technical Documentation (STED) N011R16 2008

• NBOG_BPG_2009_1 Design Dossier Examination

• NB Guidance Document
Key Pitfalls ...

Audience Participation
Responsibilities – Design / Manufacture / Subcontractors / EU Authorized Representative
Case 2

• Manufacturer A applies for CE marking for a Class III device – a surface coated knee joint replacement implant
• The uncoated implant is CE marked by US Manufacturer (with BSI), and supplied in this manner to Manufacturer A.
• Manufacturer A further processes the implant to apply proprietary coating, sterilisation and final packaging.
• Manufacturer A submits “Partial” Dossier and states that the remainder is covered by submission of US Manufacturer of uncoated knee implant
• Is this acceptable?

Submission includes:

• Description of coating, processing methods, coating characterisation
• Risk covers processing risks for the coating
• CER covers detailed biocompatibility testing of the coating
• No DoC
• IFU & labels of US MFR
Case 2: Outcome

- Submission was rejected

- No clear responsibility for the coated knee implant

- CER, Description, Risk documents all referred to ONLY the coating material and process

- Also the general content was inadequate
NB Reviewer will Check: Responsibilities

- Device descriptions, legal manufacturer, device construction and manufacture
- Manufacturing process, subcontractors
- General contents, ERs, CER, Risk management, PMS/PMCF,
- Standards (fully or partially applied)
- Declaration of Conformity
  - Does product list in technical documentation match the DOC?
- A process for generating or controlling technical documentation
Changes & Updating Key Documentation
Case 3

- Novel device (Class III) – CE application to BSI in 2013
- Dossier submitted to BSI in 2013 included 2009 RMR
- Device has undergone 2 significant design changes since original concept
  - Surgical instrumentation was incompatible with devices – observed during cadaver trials
Case 3: Outcome

- RMR was updated
- Design changes also impacted:
  - The CER. The CER was updated
  - Design specifications. Design verification studies repeated and included in 2013 submission
  - New worst case designs introduced. Sterilisation and packaging validations needed to be repeated
- Case presented pre-CE marking
- Applicable to post-CE marked devices
Reviewer will Check: Changes

- Description of the changes
- Impact on ERs, safety and performance (as intended)
- What designs, sizes, indications are covered by the change? Worst case?
- Impact and update on Risk, Clinical, PMS, performance & validation studies
- (if applicable) Update and follow-up on sales, complaints, results from PMS activities
- Manufacturer’s assessment of the change/s, conclusions and acceptability
Essential Requirements/Standards/ER Statements
93/42/EEC – Annex II:

8.2 Does not **utilise** devices derived from animal sources.

Note MDD says

- **Incorporate** in ER 8.2,
- however **utilise** in Rule 17 Annex IX & Annex II.3.
Case 4

• Technical file audit of Class IIb orthopaedic implant
• ER checklist against ER 8.2 states “No animal tissue utilised”
• PFMEA included risks relating to “fish glue” used as a polishing compound
• There were no residuals on the final product
Case 4

• Non Conformity
  • Rule 17, Annex IX is applicable (classification)
  • Utilisation of animal tissue makes device class III
• MFR argued and provided evidence on the biocompatibility of the final product – no residuals
• Appealed to MHRA
• MHRA concluded that Rule 17 was applicable
• Corrective action was accepted for MFR to find alternative source for polishing compound...
Reviewer will Check:

- Latest version of Directive?
- Review of ER checklist
  - Which ERs are applicable?
  - If applicable, how is this met – standards, procedures, test reports – PROVE IT!
- Reference to harmonised standards
  - Full or partial compliance?
- Is there a justification if not applicable?
  - Is it an acceptable justification?
  - Is it a complete justification?
Design Requirements: Verification & Validation
Case 5

- Manufacturer new to CE marking – a "virtual manufacturer"
- Class III hip joint replacement implant – a "replica" of a well known legacy system by another manufacturer
- CER based on equivalence, with PMS/PMCF plans submitted
- None of the required testing conducted. Rationale provided:
  - Good clinical performance of the equivalent legacy device
  - No concerns about mechanical failures of the equivalent system
  - Used subcontractors of the equivalent device
Case 5: Outcome

• Information provided unacceptable
• Manufacturer has no experience manufacturing this device (... or any other)
• Manufacturer strategy was to select successful product with expectation that the experience of the legacy/predicate product would “speak for itself”

• Manufacturer eventually resubmitted
Reviewer will Check: Design Verification

Design Verification

- Performance testing? If not, then why not?
- Design verification data vs. clinical data

Post production (yrs) →

Clinical data
Design verification data
Clinical Evaluation
Post Market Surveillance (PMS, PMCF, Complaints & Incidents)
Risk
Labelling and IFU
Reviewer will Check: Clinical

The reviewer will verify that clinical safety and performance data are considered satisfactory.

The information reviewed should include data from market experience of the same or equivalent devices, clinical investigations, and/or clinical evaluations and be approved by someone suitably qualified.

The manufacturer’s evaluation should:
- Follow a methodologically defined procedure
- Be actively updated with PMS

Lack of a clinical investigation must be justified for Class III/implantable devices.
Reviewer will Check: PMS

- Evidence of something proactive
- PMS review (last 3 - 5 years or since introduction), documenting at minimum complaint / vigilance history relative to devices sold
- Evidence of acceptable complaint and incident rates
- The PMS plan (consistent with clinical evaluation, risk, and lifetime of device) & implementation of that plan in renewals
- If PMCF is deemed unnecessary, an adequate rationale
Reviewer will Check: Labelling and IFU

- Check label against ER13.3
- Appropriate use of symbols – use of ISO 980/15223
- Check IFU against ER13.6

- Does intended use correspond with stated claims and clinical data presented?
- Have residual risks been warned against?
Common Non-Conformities

For Reference
Areas with Frequent Findings: TF / DD Construction

- Not clear how documentation is controlled
  - TF / DD not a controlled document
  - TF contents not all controlled or signed/dated
  - DOC date precedes date of TF
  - 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)
- No executive summary / reason for supplement not clear
- Insufficient detail in section summaries (to find or understand data)
Areas with Frequent Findings: DOC and Product Description

• Unambiguous descriptions not provided
• Product list in TF does not match DOC
• Description does not include all components
• Classification summary does not site all applicable rules and/or applicable content within rule
• No summary of design changes
• Some significant changes (design / process) not included or NB not notified in advance (class III only)
Areas with Frequent Findings: Specifications / Verification / Validation

• Design requirements not included in documentation
• Test reports included but deficient
  • Do not identify scope
  • Insufficient justification for sample size or test method selection or discussion of deviations / failures
  • Discussion not linked to requirements
  • Insufficient justification for representation of “worst case devices/testing”
• Accelerated stability testing used as basis for shelf-life but no real time testing initiated
• Product stability not considered in conjunction with package stability
• Transportation testing not conducted
• Biocompatibility assessment considers only raw materials and not manufacturing process
Areas with Frequent Findings: ERs / Standards

• Insufficient justification for ERs being N/A
• Lifetime (ER 4, life in use) confused with Shelf-life (ER 5 / 7.2, life prior to use) ... lifetime not identified
• Standards not referenced for all pertinent ERs (e.g. performance standards not referenced for ER 13 even though there are specific labelling requirements)
• Relevant harmonized standards not referenced
  • Confusion between harmonized vs. other standards
  • Presumption of conformity / Z Annex
• Level of compliance to harmonized standard not identified (full or partial)
  • If full compliance to harmonized standard not claimed, no gap analysis provided relative to ability of solution to meet ERs
Areas with Frequent Findings: Manufacturing / Sub-Contractors

• No description of manufacturing flow (i.e. flowchart) w/subcontractor and inspection requirements

• Manufacturer cedes authority of purchased parts / services to OEM / sub-contractor when legally responsible
  • Insufficient understanding of processing aids / materials utilized during manufacturing
  • Does not determine safety / performance of entire device
Areas with Frequent Findings: Labels and IFUs

• Medical purpose not clear in IFU – Must meet Article 1
• Non-harmonized symbols used in labelling (including some in EN ISO 15223-1 per notes) not defined
• Labels do not adequately identify device / contents to non-English speaking users
• Claims on websites / promotional material not supported by data or imply use outside indications
Areas with Frequent Findings: Risk Management

• Normative elements of ISO 14971 (RMP, RA, RMR) not all included
• Deviations from EN ISO 14971:2012 not addressed
• All risks (i.e. design, process, application) not considered
  • Process risks frequently not included if subcontracted
  • Review of subcontracted risks not evaluated by manufacturer for completion or agreement
  • Clinical risks not included
• RMF not actively updated / PMS not integrated into RMF
Areas with Frequent Findings: CER / PMS / PMCF

• Clinical evaluation reports not provided
• Clinical Investigation not provided (for implants / class III) and not duly justified
• Clinical data not provided for all indications or justified based on representative data
• Clinical investigation not carried to full term or deviations justified
• Impact of design changes not addressed in CER

• CER attests “safety and efficacy” rather than “safety and performance as intended”
  • efficacy: ability of device to produce a desired effect
• CER does not cross-reference RMF
• No device / family-specific PMS Plan
• No PMCF when CER approved based on equivalence
• EU / WW sales history not provided with summary of complaints / vigilance over same period
Summary
Manufacturer’s Role

• Manufacturer should have evidence and be able to summarise data which supports the conclusions drawn
• Meet ERs or has justifications why “N/A”
• Fit for purpose? i.e. not just “meets harmonised standards” (most innovative manufacturers usually ahead of the “state of the art”)
• Positive risk/benefit analysis?
• Conclusions are based on clinical data
• Reliance on data on other devices needs clear justifications & evidence
Technical Documentation Review: NB’s Role

• Ensure that the manufacturer’s conclusions are sound
  • ... and based on evidence
• Cannot draw conclusions based on data presented by the manufacturer
• Cannot tell manufacturer how to arrive at the answer
• NB may call in other specialist expertise ... as/if required
  • Clinician, biostatistician, animal tissue expert, medicinal expert, toxicologist etc...
Conclusions

• Do not assume prior knowledge of your product
  • The Notified Body cannot assume, interpret or conclude for the Manufacturer

• Know what is required... and expected... from your NB
  • If in doubt... ask

• Try to do more than the minimum...