Writing In-House Medical Device Software in Compliance with EU, UK, and US Regulations

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<< *Supplementary material* >>

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www.softwaremedicaldevice.org.

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[1] The book itself can be purchased from this website, as well as from other main booksellers.

Contents

1. Introduction

As mentioned in Section 1.6 of the book, this *Supplement* is designed to be read in conjunction with the printed publication. It contains material that could not be fitted into the tight constraints of a printed publication, just missed the production deadline, or refers to documents published after the deadline (October 2023). The additional material refers to the relevant Chapter/Section in the book.

As will be evident, this document is a work-in-progress that will be periodically updated to reflect changes in regulations, standards, and guidance. Each section contains a brief summary of the referenced material, but the full text can be read by simply following the appropriate link.

The first version of this document to be made publicly available (in March 2024) was actually version 2.4. This new version (2.5) represents the first update. The main changes are referenced in the summary at the end of the document. Apart from providing useful updates on selected topics, perhaps the most practical use of the document will be the inclusion of clickable hyperlinks for all the web references given in the book, which would avoid readers having to type complex URLs into web browsers.

The structure of this document is topic-based, so different regulatory approaches (EU, UK, US) to a given issue will be covered where appropriate.

2. Risk controls

2.1. Risk control measures external to the software

Reference in the text: Section 5.4.1.4 (Software safety classification)

Risk control measures (RCM) *external* to the software may include physical systems (separate hardware or software) as well as *procedures* performed by healthcare professionals that may mitigate any harm caused by the failure/malfunction of the specific medical device software under development. This relates to documented intended use and intended users. For example, diagnostic software that may assist in the diagnosis of disease X is stated not to be used as the sole means of making a diagnosis.

Other external RCMs would include systems and/or software that check the accuracy/validity of the software in the field (e.g., external audit schemes). Note that such systems are separate from any final product testing performed by the manufacturer, which is deemed internal to the software development process.

If the external RCMs are comprehensive to the point where a software failure could not conceivably result in harm to a patient, then the software can be classified as Class A and be subject to less rigorous software engineering. However, if a manufacturer relies on an RCM-based 'safety argument' to reduce the software safety classification he must be able to verify the effectiveness of such measures 'in the field'.

3. Medical device software

3.1 MDCG guidance on MDSW-hardware combinations

Reference in the text: Section 6.3.4.5 (Wearable devices)

The MDCG has recently issued guidance on the qualification and conformity assessment of MDSW (mostly apps) that is intended to work with hardware or 'hardware components' (e.g., external sensors or hardware components built into smartphones).
https://health.ec.europa.eu/system/files/2023-10/md_mdcg_2023-4_software_en.pdf

It contains some useful information but has also been criticised for its lack of clarity on key regulatory questions.
https://www.johner-institute.com/articles/regulatory-affairs/mdcg-2023-4/

3.2 Software classification according to IEC 62304

Reference in the text: Section 5.4.1

More on software classification:
https://www.johner-institut.de/blog/iec-62304-medizinische-software/sicherheitsklassen-iec-62304/

This article was written in December 2017 but is still relevant. Note that some figures are in German.

For a general review ("Software and IEC 62304"):
https://www.johner-institut.de/blog/category/iec-62304-medizinische-software/

3.3 Coding standards

Reference in the text: Sections 5.4.4, 8.5.

Although the article below was written quite a long time ago (December 2016) it contains a concise summary of the reasons for employing coding standards to fulfil the software life cycle requirements of MDR 17/745 and reiterates many of the points made in the book.
https://www.johner-institut.de/blog/iec-62304-medizinische-software/kodierrichtlinien-iec-62304-fda/

3.4 "Intended use" and "Indications for use"

Reference in the text: Sections 6.3.12.1, 6.5.3.1, 6.5.8.4.

More on the difference between these two terms:

https://www.meddeviceonline.com/doc/key-considerations-in-intended-use-and-indications-for-use-statements-for-medical-devices-0001 (14 December 2023).

3.5 In-house development of medical software

3.5.1 The Role of (UK) Clinical and Scientific Computing staff

Reference in the text: Section 2.6.2

The UK Institute of Physics and Engineering in Medicine (IPEM) has issued a Policy Statement on the *Role of Clinical and Scientific Computing in Medical Physics and Clinical Engineering*: https://www.ipem.ac.uk/media/emvlmlak/role-of-clinical-and-scientific-computing-feb-2024.pdf (issued 21 February 2024).

It is stated (in the *Software Engineering* section) that "The need for Healthcare Scientists who can develop and maintain software used within a clinical environment is the leading driving force behind the formation of Clinical and Scientific Computing teams". The defined software engineering roles include "Developing in-house medical device software, following best practice, for example IPEM best practice guidance [*link below*] and the standards it contains". https://www.ipem.ac.uk/media/vp0ewy01/ipembe-1.pdf

3.6 Spreadsheet development and testing

3.6.1 Lessons from the financial sector?

Reference in the text: Section 5.4.5

Although the intended purpose of financial software is obviously very different to that used in the medical domain, spreadsheet guidelines developed for the finance industry cover mainly basic principles that are universally applicable.

Large finance companies undertake a considerable amount of in-house software development (mostly spreadsheets), which comprises development by dedicated IT professionals in a central IT department as well as development by 'other staff' in more front-line roles. The latter type is generally undertaken by talented self-taught software developers with little or no formal training, and is referred to as End-User Computing (EUC).

The acronym is somewhat ironic as EUC stands for *equipment under control* is health and safety circles. Most 'mission critical' applications are generally developed by the central IT team, but one large bank admitted (in 2009) to having "approximately five times the number of critical EUC applications as those that would be classified as "SOX Tier-1" applications[2].

[2] SOX refers to the Sarbanes-Oxley Act, passed by the US Congress in 2002 in response to serious fraud scandals in the financial sector in the US. The implications for spreadsheets used by large companies for financial reporting were discussed by Panko and Ordway in 2008: https://arxiv.org/ftp/arxiv/papers/0804/0804.0797.pdf

Regarding in-house software development, organisational parallels between large health institutions and large financial institutions are limited (central IT departments in large hospitals do *not* generally develop software, and certainly not medical software), but it is interesting to read how a large bank recognised the importance of EUC and developed policies and procedures to help ensure that it was conducted within a more controlled environment.
https://arxiv.org/ftp/arxiv/papers/0909/0909.2455.pdf

3.6.2 Spreadsheet testing

Reference in the text: Sections 2.2.2, 3.3.3, 5.4.5

The book discusses software engineering process techniques to reduce the probability of introducing errors into spreadsheets but it must be assumed that some errors will remain. As for any other types of software, spreadsheet testing is therefore crucial to find and eliminate these 'residual bugs'.

Panko R. Spreadsheet Errors: What We Know. What We Think We Can Do.
https://arxiv.org/abs/0802.3457

In the above seminal 2008 publication Ray Panko made the case that cell-by-cell code inspection is the more reliable and efficient way to uncover spreadsheet errors. In a related 2015 presentation, Panko considered what we *don't* know about spreadsheet errors, which includes discussion of relevant research on human cognition.
https://eusprig.org/wp-content/uploads/1602.02601.pdf

3.7 Clinical information systems

Hospital Information Systems (HIS)
Radiology Information Systems (RIS)
Laboratory Information [management] Systems (LIMS)
Patient Data Managements Systems (PDMS)

PDMS is a special case and could qualify as a medical device. For more information see:

https://www.johner-institut.de/blog/tag/informationssysteme/

https://www.johner-institut.de/blog/gesundheitswesen/pdms/

Original reports in German but your web browser will easily translate.

4. Quality management systems

4.1 Recommended eQMS tools

Reference in the text: Section 5.2 (Quality management)

A 'software vendor checklist' produced by the Greenlight Guru company may be used as the basis for an eQMS tender document:
https://www.greenlight.guru/downloads/qms-software-vendor-checklist

4.2 Quality manual template

Reference in the text: Sections 5.2.1.2, 5.2.1.5, 5.2.2.

For those starting from scratch with formal QMS, a useful free template is available from Greenlight Guru:
https://www.greenlight.guru/downloads/quality-manual-template

4.3 FDA formalises the move from QSR to QMSR

Reference in the text: Sections 6.5.6, 9.2.1.3

The FDA has published its 'final rule' amending the Quality System Regulation (QSR) to better align with ISO 13485:2016. The title of 21 CFR Part 820 will change from QSR to Quality Management System Regulation (QMSR). The enforcement date for compliance with the new regulation is 2 February 2026:
https://www.greenlight.guru/blog/fda-qmsr-final-rule

5. Cybersecurity

5.1 Legacy devices

Reference in the text: Sections 6.3.6.7, 6.5.8.1; Chapter 8

There is recent guidance from the MITRE Corporation[3] about managing cybersecurity risks for "legacy devices". MITRE is a not-for-profit organisation that performs research for the FDA and other US government agencies. Its guidance may be regarded as complimentary to established IMDRF guidance as it is more focused on the end-user. The guidance applies to managing medical devices that were not originally designed according to modern cybersecurity principles.
https://www.mitre.org/sites/default/files/2023-11/PR-23-3695-Managing-Legacy-Medical-Device%20Cybersecurity-Risks.pdf (November 2023).

[3] MITRE is not an acronym, but the name given by one of the founders of the company in the 1950s.

https://www.imdrf.org/sites/default/files/2022-05/IMDRF%20Cybersecurity%20proposed%20document%20PDF.pdf (May 2022)

5.2 Finalised FDA cybersecurity guidance 2023

Reference in the text: Section 6.5.8.11

In September 2023 the FDA finalised its guidance on cybersecurity of medical devices[4]. The guidance is similar to the April 2022 draft, but it provides more detail on conducting cybersecurity risk assessments, interoperability considerations, and documents to be included in premarket submissions.
https://www.fda.gov/media/119933/download (27 September 2023).

A gap assessment checklist has been developed by Greenlight Guru to help in the implementation of the new (2023) FDA guidelines on medical device cybersecurity:
https://www.greenlight.guru/downloads/cybersecurity-gap-assessment-checklist

The final guidance also rests on a new statutory authority explicitly authorizing the FDA to (a) require cybersecurity information be included in medical device submissions for "cyber devices" and (b) require manufacturers to take actions to demonstrate reasonable assurance that such devices and related systems are "cybersecure."
https://www.ropesgray.com/en/insights/alerts/2023/10/fda-finalizes-guidance-on-medical-device-manufacturer-cybersecurity-responsibilities

https://www.meddeviceonline.com/doc/understanding-the-fda-s-new-medical-device-cybersecurity-guidelines-0001

5.3 CISA's strategic plan

The Health Sector Coordination Council (HSCC) of the US Cybersecurity and Infrastructure Security Agency (CISA) has published a revised 5-year strategic plan (2024-2029).
https://healthsectorcouncil.org/JSP2

It is suggested that manufacturers may use this document to compliment IEC 81001-5-1 and, as such, it may have a bearing on what is considered "state of the art" for the IT security of health-related equipment, including medical devices.
https://25622905.hs-sites-eu1.com/how-important-the-regulatory-overview-is

The plan represents a huge collaborative effort of over 400 organisations (US healthcare providers and pharmaceutical/medtech companies) and several government agencies, including the FDA. It is therefore likely that the revised plan will influence future FDA guidance on cybersecurity of medical devices. It may also influence future MDCG cybersecurity guidance (ref: EU MDR) as the current document is rapidly becoming outdated.

[4] FDA concerns about cybersecurity issues associated with medical devices all started with the 2017 WannaCry ransomware attack (see Section 8.1 of the book).

5.4 Software Bill of Materials

Reference in the text: Sections 6.3.6.7, 6.5.8.11, 8.1, 8.2.5, 8.5.1

As explained in the book, the Software Bill of Materials (SBOM) plays an important role in the management of cybersecurity vulnerabilities. The link below contains information on SBOMs in relation to regulatory requirements and common data formats:
https://www.johner-institut.de/blog/iec-62304-medizinische-software/sbom-software-bills-of-materials/

It is pointed out in the Johner Institute article that MDR 17/745 does not *specifically* require a SBOM (Annex I, Section 17.2), but does require IT security according to the 'state of the art'. SBOMs *are* the state-of-the-art, QED.

In contrast, SBOMs are a specific FDA requirement in the US, as described in 'Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions', September 2023 (see Section 5.2).

5.4.1 Use of SBOMs

OK, you have produced an accurate SBOM, now what do you do with it? Essentially, the SBOM acts as the *input* to the wider process of identifying cybersecurity vulnerabilities. Each software component in the SBOM inventory must be checked for possible threats using a national/international cybersecurity database and appropriate action taken (usually in the form of a security patch) if the matching process uncovers potential issues.

In the US, the national repository is the National Vulnerability Database (NVD). To make the matching process manageable, an SBOM with numerous entries must somehow be integrated into the organisation's vulnerability management process (as described in its cybersecurity policy).

https://nvd.nist.gov/
https://www.crowdstrike.com/cybersecurity-101/secops/software-bill-of-materials-sbom/

The cybersecurity policy is particularly important here because there must be a documented means of prioritising the actions for resolution of the identified vulnerabilities (there could be many!); a process typically based on assigned severity (look up CBSS score), perceived risk, exploitability, and ease of fix. Clearly, if an available security patch could fix several identified security issues, then that would get priority. The NVD uses the common vulnerability scoring system (CVSS) to represent the severity of an information security vulnerability. A score on a scale of 0-10 is assigned for all published common vulnerability and exposures (CVE) records:

CVSS v3.x Ratings

Severity	CVSS score
None	0.0

Low	0.1 - 3.9
Medium	4.0 - 6.9
High	7.0 - 8.9
Critical	9.0 - 10.0

The CVSS is not a measure of risk, which should be assessed separately.

https://nvd.nist.gov/vuln-metrics/cvss
https://www.balbix.com/insights/understanding-cvss-scores/

The CVSS is a useful severity measure but does not tell you how exploitable (by hackers) a particular venerability might be. The NVD promotes the use of a semi-quantitative scoring system to assess exploitability of a particular vulnerability (i.e., the Exploit Prediction Scoring System, EPSS) to further assist a medical device manufacturer in prioritising actions. The EPSS is effectively a probability measure so the metric scale is 0-100%.
https://www.bringa.com/glossary/what-is-epss-score/

The US Cybersecurity and Infrastructure Security Agency (CISA) maintains a up to date list of cybersecurity vulnerabilities that are *known* to have exploited by cybercriminals 'in the wild'. This known exploited vulnerabilities (KEV) repository is known as the 'CISA KEV list'.

Although there is no prescribed best practice method for prioritising actions for a list of identified vulnerabilities, it is reasonable to suggest that an algorithm/filter of the following nature might be used.

IF (CVSS > x. AND/OR EPSS > y. OR present on the CISA KEV list), THEN DO P

Where P is an urgent remedial action.

Clearly, even if a vulnerability has an CVSS of 8.0 but an EPSS of 0% (i.e. not yet exploited in the field so not on CISA KEV list) then it would generally be considered low priority for urgent action. The general approach must be tempered by a risk assessment that considers the likelihood that a vulnerability having a high CVSS *and* a high EPSS could cause harm to a patient (directly or indirectly) if the vulnerability was exploited to the extent that affected device functions were compromised.

5.4.2 EU cybersecurity vulnerabilities databases

A recent (January 2023) update to the Network and Information Security (NIS2) Directive tasked the European Agency for Cybersecurity (ENISA) with establishing and maintaining an EU cybersecurity vulnerability database.

Although the Agency is still establishing the policies and procedures around this database to ensure its security and integrity, the EC is favouring a decentralised system whereby manufacturers disclose vulnerabilities to the National Computer Security Incident Response Team (CSIRT) in the country in which they are based.
https://therecord.media/eu-rejects-requirements-for-manufacturers

The EU Cybersecurity Resilience Act (CRA), which codifies the above reporting system (amongst other duties of manufacturers) is set to become law in the EU in April 2024.
https://digital-strategy.ec.europa.eu/en/policies/cyber-resilience-act
https://www.insideprivacy.com/cybersecurity-2/the-cyber-resilience-act-is-one-step-closer-to-becoming-law/

5.5 EU Cybersecurity Resilience Act

Reference in the text: Section 6.3.6.7.

The EU Cybersecurity Resilience Act (CRA) is in active development and is due to become law in 2026 or 2027.

https://spyro-soft.com/blog/cybersecurity/the-cybersecurity-resilience-act-cra

In principle, the CRA will apply to "all products with digital elements", but a limited number of product categories that are already considered to be sufficiently regulated (*including* medical devices, automotive vehicles and aviation products) will be exempt from the regulations.

https://www.fieldfisher.com/en/insights/update-on-the-eu-cyber-resilience-act-for-uk-companies#

6. Artificial intelligence/machine learning

6.1 EU AI Act

6.1.1 The legal process

Reference in the text: Sections 7.2.3, 9.3.3.

The EU AI Act has now been unanimously endorsed the 27 member states, thus affirming the political agreement reached in December 2023. The Act faced technical revisions for over a month due to its complexity, but remaining concerns were finally resolved upon the adoption of the AI Act by the Committee of Permanent Representatives on 2 February 2024.

The 27 member states approved the legislation on May 21, 2024, so that it can come into force after publication in the Official Journal of the EU and a further 20-day period. The EU AI Act was finally published in the Official Journal of the EU on 12 July 2024 and came into force on 1 August 2024. https://eur-lex.europa.eu/legal-content/DE/TXT/?uri=OJ:L_202401689

However, various transition periods are allowed for manufacturers to get fully up to speed with the new regulations:

February 2025: Regulations on prohibited AI systems become applicable.

August 2025: Obligations for General Purpose AI (GPAI) systems become applicable, excluding fines.
August 2026: All provisions of the AI Regulation apply, except for Article 6 paragraph 1 AI Regulation (classification rule for high-risk AI systems according to Annex I)

The Act called for the establishment of a ***European AI Office***, which came into force on 21 February 2024. The tasks specified for the institution include:

- Developing tools for assessing the capabilities of general-purpose AI models.
- Monitoring the implementation of the new rules.
- Identifying emerging risks, investigating potential infringements, and supporting the enforcement of regulations on prohibited AI practices and high-risk systems.

The AI office will collaborate with relevant bodies under sectoral legislation, facilitate information exchange between national authorities, and maintain databases of when general-purpose AI models are integrated into high-risk AI systems.

6.1.2 Definitions

Reference in the text: Sections 7.2.3, 9.5.5.1.

The EU AI Act is now available in an almost 900-page document that is somewhat difficult to read. In particular, there has been some concern regarding the new definition of "AI system":

"An AI system is a machine-based system designed to operate with varying levels of autonomy and that may exhibit adaptiveness after deployment and that, for explicit or implicit objectives, infers, from the input it receives, how to generate outputs such as predictions, content, recommendations, or decisions that can influence physical or virtual environments."

The final version of the AI Act contains a more specific qualification of medical devices as "high risk AI". Namely, AI-enabled medical devices are considered high risk if:

(i) they are intended to be used as a safety component of a product, or if they themselves are a product covered by the Medical Device Regulation (EU) 2017/745 (MDR) or by the In Vitro Diagnostic Regulation (EU) 2017/746 (IVDR) **and**

(ii) the relevant product is required to undergo a third-party conformity assessment pursuant to the MDR or the IVDR. This does also apply if the AI system is placed on the market or put into service independently from the relevant product.

As the vast majority of AI systems used in medical devices fulfil these conditions, most AI systems applied in medical devices would be categorized as "high-risk" under the EU AI Act.
https://www.allenovery.com/en-gb/global/blogs/tech-talk/what-are-the-legal-implications-of-european-ai-regulations-for-medical-device-companies

https://www.taylorwessing.com/en/insights-and-events/insights/2023/09/medical-devices

6.1.3 General content

Reference in the text: Sections 7.2.3, 9.5.5

Compliance is required by all providers, distributors or deployers of AI systems and models within the EU or marketed into it. The degree of regulation is risk dependent, with four levels ranging minimal to unacceptable. Special obligations apply to generative and general-purpose AI depending on whether the model is open source or not.

The following guidance document offers three use cases to illustrate compliance considerations: 1) spam filters as low-risk, 2) artistic deep fakes as low-risk with disclosure requirements, and 3) credit scoring as high-risk requiring stringent compliance due to potential discrimination.
https://media.francedigitale.org/app/uploads/prod/2024/02/01162803/Compliance-AI-Act-Feb-24.pdf (February 2024).

6.1.4 Implications for medical device manufacturers

The Johner Institute has produced a useful summary of the implications of the EU AI Act for medical device manufacturers:
https://www.johner-institute.com/articles/regulatory-affairs/and-more/eu-data-act-cards-on-the-table/ (30 November 2023)

One of the important things highlighted in the article is that the controversial data-sharing requirements described in Chapter II of the Act do not apply to micro or small enterprises. According to EU Recommendation 2003/361/EC, these are enterprises that employ fewer than 50 persons and whose annual turnover and/or annual balance sheet total does not exceed EUR 10 million.

Following the final approval of the EU AI Act, work is now underway to produce guidelines for its adoption, including the medical devices sector. Watch this space!

6.1.5 The position of open-source AI

The position of open-source software was a contentious issue in the drafting of the new regulations, some feeling that the general approach to open source was too relaxed (AI Act Newsletter, 30 April 2024), while others held a different view. The situation was not helped by the inclusion of a serious error in the originally published draft regulations, which indicated that true open-source AI would not be exempt from the provisions of the Act – exactly the opposite of what was originally intended.

The history of how the EU AI Act was developed, with particular reference to open source has been usefully documented by the Open Future Group:
https://openfuture.eu/observatory/aia-open-source/

In the end, the regulations contain a limited exemption for open-source software, depending on whether it is contained in an AI system or a General-Purpose AI Model:

https://www.orrick.com/en/Insights/2024/05/The-EU-AI-Act-Open-Source-Exceptions-and-Considerations-for-Your-AI-Strategy#

As the exemption for open-source will *not* generally apply if the software is incorporated into "high risk systems", manufacturers of complex software-based medical devices may not be able to make use of the exemption. Further clarification from EU medical devices regulators is awaited.

6.1.6 Codes of Practice

Reference in the text: None

See EU AI Act Newsletter 56, 08/07/24

Article 56 of the Act establishes Codes of Practice as a temporary means compliance for GPAI model providers. These codes are intended to bridge the gap between the point at which provider obligations take effect and when formal standards are adopted (3+ years later). While voluntary, adhering to these codes presumes conformity with Articles 53 and 55 obligations. Providers not following the codes must prove compliance by other means.

On an indirectly related issue, note that the adoption deadline for most of the *harmonised* standards required for the *EU MDR* have been put back until May 2028 (see 14.1).

6.2 Diagnostic Assistance Levels (DALs)

Reference in the text: None.

The article below (from authors in Japan) contains a proposal for a risk-based classification system for AI-based computer-aided diagnosis software used in radiology. The proposed system has 5 levels (DL1 to DL5) and is perhaps something that the IMDRF may consider in due course. The adoption of such a system would avoid the majority of AI-enabled medical devices being classified as "high risk" under the new EU AI Act (see 6.1.2).
https://www.jstage.jst.go.jp/article/abe/7/0/7_7_118/_article/-char/en (2018)

6.3 Data quality

Reference in the text: Section 9.5.5.2

The EU Data Act was passed in early December 2023.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM%3A2022%3A68%3AFIN

One of its goals is to promote economic growth through improved availability of data, but that requires interoperability and the willingness to share this data. The ways in which the EU Data Act may affect medical device manufacturers are discussed in the article below: https://www.johner-institut.de/blog/regulatory-affairs/eu-data-act/ (5 February 2024)

6.4 FDA's Predetermined Change Control Programme (PCCP)

Reference in the text: Section 6.5.8.9 (Devices containing AI technology)

Regarding post-market changes, a series of recent articles in *Med Device Online* provide further detail on what the FDA will expect from manufacturers of AI-based medical devices in the context of its PCCP.

Part 1: https://www.meddeviceonline.com/doc/medical-device-postmarket-change-controls-fda-k-software-modification-guidance-0001

Part 2: https://www.meddeviceonline.com/doc/deciphering-new-u-s-laws-around-predetermined-change-control-plans-0001

Part 3:https://www.meddeviceonline.com/doc/samd-pccp-implementation-beyond-ai-ml-considerations-challenges-0001

Although the FDA consider PCCP to be the way forward for dealing with AI/ML-enabled medical devices, the legal position was, until recently, unclear. However, since March 2023 the FDA now has *statutory authority* to consider PCCP in its review of all device submissions. On December 29, 2022 Section 3308 of the Appropriations Bill of 2023 amended the Food, Drug & Cosmetic Act (FD&C) to include Section 515C ("Predetermined Change Control Plans for Devices"), which authorizes the FDA to consider PCCPs while reviewing submissions under PMA, PMA supplement or 510(k). The amendment to the Act became law on March 29, 2023, along with the amendment in Section 524B focused on the cybersecurity of medical devices.

The amendment means that a device *subsequently modified* according to an established PCCP may not be used as a predicate for future (510(k)) submissions. In other words, only the version of the device cleared or approved *before* any changes made under the PCCP may be used by a sponsor as a predicate device.

6.5. Foundation models

Reference in the text: the term 'foundation model' is not used in the text, but related issues are covered in the AI sections of Chapters 6 and 9.

Foundation models represent the 'next wave' of AI technology and may replace the task-specific models that have been developed over the last 5 years. They are so-called because their design means that they can be as the foundation for many applications of the basic model with minimal fine tuning. Examples include GPT-4 and BERT. Such systems can generate

a coherent output (e.g. an essay or graphic) from a short prompt, even if the model was not specifically trained on how to generate the text/image etc. in that way.

Rishi Bommasani, the Society Lead at the Stanford Center for Research on Foundation Models, has suggested a tiered approach to the categorisation of foundation models that may lead to proportionate regulation. This is relevant in the context of the EU AI Act (Section 6.1). https://crfm.stanford.edu/2023/11/18/tiers.html (2021).

The complex legal issues surrounding foundation models and 'general-purpose AI' (GPAI) – also known as 'artificial general intelligence' (AGI) (see Section 9.5.5.1 of the book) are considered in the context of the EU AI Act in the article below: https://ai-regulation.com/regulating-foundation-models-in-the-ai-act-from-high-to-systemic-risk (January 2024).

6.6 Machine Learning Good Practice (MLGP) Guidelines

Reference in the text: Sections 3.3.4, 9.5.5.

10 basic principles of MLGP have been identified in joint statement from the US FDA, the UK MHRA and Health Canada, which was published in 2021:

https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles

The links below provide brief commentaries on the above guidance.
https://www.meddeviceonline.com/doc/ml-powered-medical-devices-tips-for-regulatory-compliance-0001

https://www.meddeviceonline.com/doc/the-guiding-principles-of-gmlp-identified-by-the-fda-hc-and-mhra-0001

The FDA issued an updated document in June 2024 that is generally more detailed and particularly elaborates on principles 7 and 9 from the first document.

https://www.fda.gov/medical-devices/software-medical-device-samd/transparency-machine-learning-enabled-medical-devices-guiding-principles

The IMDRF has recently (June 2024) issued it own *draft* guidelines for the use of ML for medical device development that is word-for-word identical to the 10 principles issued by the FDA/Health Canada/UK MHRA in 2021.

https://www.imdrf.org/consultations/good-machine-learning-practice-medical-device-development-guiding-principles

Bizarrely, there is no reference to the above 2021 FDA publication in the IMDRF document. I do not understand this. The closing date for comments on the draft is 30 August 2024.

6.7 Regulatory issues with generic LLMs

Reference in the text: Section 9.5.5

LLM: Large language model.

Commonly used Generic chatbots include OpenAI's ChatGPT, Google's Gemini, and Microsoft's Copilot (formally Bing Chat).

6.7.1 Is ChatGPT a medical device?

A German law firm has claimed that ChatGPT should be considered a medical device and has sought clarification from the German regulator.
https://e-health-com.de/details-news/vorberglaw-fordert-regulatorische-klarheit-fuer-chatgpt-im-bereich-digitaler-medizinprodukte/ (7 November 2023).

This was highlighted in a *Medical Device Briefing* (Issue 38/23) published by the Johner Institute on 28 November 2023, in which the claim was disputed, based on the intended purpose of ChatGPT. According to its Terms of Use, OpenAI does not intend its products to be used for medical diagnostic or therapeutic purposes:

"*You must not use any output relating to a person for any purpose that could have a legal or material impact on that person, such as making credit, educational, employment, housing, insurance, legal,* ***medical****, or other important decisions about them*".

https://openai.com/policies/terms-of-use (31 January 2024)

6.7.2 Using LLM-based chatbots (such as ChatGPT) in accordance with Data Protection Regulations:

A good summary of this topic can be found here:
https://datenschutz-hamburg.de/news/checkliste-zum-einsatz-llm-basierter-chatbots

6.7.3 Using generative AI technology for interrogating international standards

In principle, generic or more specific AI tools may be used to search for answers to specific questions about international standards. The more specific tools tend to be a combination of a proprietary knowledge base (built by the company marketing it) and an LLM. The argument for dedicated system is that the data going into them is much more carefully vetted than the tens of millions of data items (trawled from the general internet in a *relatively* uncontrolled fashion) being input to generic ("ask me anything") systems such as ChatGPT. Better data in, better answers out, to put in simply. The 'rub', of course, is that general tools such as Gemini and ChatGPT are free to use; proprietary tools are not. For example, Advisera has developed a generative AI tool for extracting information from some of the main ISO management standards: https://advisera.com/experta/

6.7.4 Regulatory issues and controversies surrounding LLMs used in healthcare

Reference in the text: Sections 6.3.6.5 (EU), 6.4.4.3 (UK), 6.5.8.9 (US), 9.5.5.5

A comprehensive review of what was referred to as the "regulatory ambiguity" of generic LLMs applied in the healthcare field was published (as Viewpoint article) in *The Lancet* in September 2024:

Freyer O, et al. A future role for health applications of large language models depends on regulators enforcing safety standards. *The Lancet Digital Health*, 6: 9: E662-672, September 2024.
https://www.thelancet.com/journals/landig/article/PIIS2589-7500(24)00124-9/fulltext

6.8 AI in Medical Physics - Roles and responsibilities of medical physicists

Reference in the text: Section 2.6.1

The International Atomic Energy Agency (IAEA) has recently published a guidance document on "Artificial Intelligence in Medical Physics - Roles, Responsibilities, Education and Training of Clinically Qualified Medical Physicists".
https://www.iaea.org/publications/15450/artificial-intelligence-in-medical-physics (2023).

6.9 Notified Bodies Guidelines on AI (5th edition).

Reference in the text: Section 6.3.6.5

Created by the German Notified Bodies Alliance (IG·NB), this document takes the form of a checklist for use by EU Notified Bodies and other interested parties. Version 5 was published on 15 December 2023.
https://www.ig-nb.de/?tx_epxelo_file%5bid%5d=1003235&cHash=f03bcf63e76d99d4ca5b51957cff7f69

Crucially, each question contains a reference to a clause in a standard indicating how the requirement might be achieved. The checklist/questionnaire is based, in part, on the "Guideline for AI for Medical Devices" by Johner, Molnar et al [see Reference List, Chapter 6, ref 33].

6.10 Validation standards for the application of AI within a healthcare setting

Reference in the text: Section 9.3.3

There is a new British Standard that is being adopted/encouraged within some UK clinical departments, either as a development guide or, in a procurement setting, as a specification that potential commercial suppliers would be required to comply with. The standard comprises a set of auditable clauses so can be used to conduct conformity audits leading to certification.

https://knowledge.bsigroup.com/products/validation-framework-for-the-use-of-artificial-intelligence-ai-within-healthcare-specification?version=standard

The standard takes a top-level view of the term *validation*, providing a set of requirements for 'key evaluation criteria' such as clinical benefits, standards of performance, successful and safe integration into the clinical work environment, ethical considerations, and socially equitable outcomes from system use.

6.11 Standards to support the development of AI-enabled medical devices

Two standards are being developed to guide how *risk management* techniques should be applied to AI-enables medical devices:

ISO 23894:2023: Information technology – Artificial intelligence – Guidance on risk management. (*This is a generic standard based on ISO 31000:2018*)

BSI AAMI 34971:2023: Application of ISO 14971 to machine learning in artificial intelligence.

In connection with the new EU AI Act, CEN/CENELEC is busy working on a wide range of standards that will support its implementation. The European Trade Union Organisation (ETUC) publishes a newsletter containing updates and progress reports from the various working groups.

https://etuc.org/sites/default/files/page/file/2024-05/AI%20standardisation%20Inclusiveness_Newsletter3.pdf

6.12 Product liability considerations for AI-enabled medical devices

Reference in the text: Section 7.3.2

https://www.meddeviceonline.com/doc/product-liability-considerations-for-ai-enabled-medtech-0001

The above article is written by US lawyers from the perspective of avoiding and defending product liability claims. Some definitions relate specifically to US law, but the general principles are equally applicable to EU Product Liability Laws.

In September 2022, the EC published a *proposal* for a Directive on AI Liability, on the basis that "Current national liability rules, in particular based on fault, are not suited to handling liability claims for damage caused by AI-enabled products and service". The Directive itself has not appeared yet, but the proposal can be read here:

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX%3A52022PC0496&utm_campaign

6.13 General ethical and regulatory challenges for the medical community

Reference in the text: 6.4.4.3

Viewpoint article (April 2024): Ethical and regulatory challenges of large language models in medicine:
https://www.thelancet.com/journals/landig/article/PIIS2589-7500(24)00061-X

Editorial (August 2024): Balancing AI Innovation with patient safety:
https://www.thelancet.com/journals/landig/article/PIIS2589-7500(24)00175-4/fulltext

The above Editorial calls on the UK government to urgently introduce "comprehensive AI regulations tailored to the health-care sector".

6.14 The UK's sandbox for healthcare AI development

Reference in the text: Section 6.4.4.3

The MHRA has recently announced the establishment of a regulatory sandbox project, referred to as the "AI Airlock", which started in pilot form in May 2024.

https://www.gov.uk/government/collections/ai-airlock-the-regulatory-sandbox-for-aiamd

Its aim is to provide a "safe space" to trial innovative healthcare AI products before they are formally implemented. Its main distinguishing feature is the plan to involve *all* interested parties. A stated aim is to further clarify the distinction between AI as a *medical device* (AIaMD) and other health technologies that use AI. The phrases *Digital Medical Devices* and *Digital Health Products* and have also started to appear in the literature:

https://www.meddeviceonline.com/doc/the-ai-medical-devices-revolution-unlimited-potential-amid-regulatory-challenges-0001

7. Clinical evaluations and clinical investigations

Reference in the text: Sections 6.3.10, 6.5.5

This article provides a brief summary of the main regulatory (FDA, EU) requirements for clinical evaluations and clinical investigations, with reference to relevant standards. The website referenced below also contains access to the output from the Q&A session at the associated webinar held in 2023.
https://www.greenlight.guru/blog/navigating-clinical-evaluations-and-investigations-in-medtech (12 January 2024)

8. Staffing levels

8.1 Minimum staffing levels in small organisations

Reference in the text: Sections 2.6.2, 2.7; Chapter 2: Appendix1, Section 6.3.7.1.2.

There is a famous *US Navy Seal* saying: "Two is one and one is none", which applies to small combat teams.
https://preparednesshub.com/two-is-one-and-one-is-none-the-art-of-redundancy/

The idea simply means that only having one of something is *effectively* the same as not having it at all, and having two of something is the same as what you think having one means. It applies equally well to small teams working in industry and commerce, including lone programmers working in clinical departments. The saying is referred to in a Greenlight Guru paper on managing design controls using spreadsheets, which discusses the concept of a single point of failure, and the desirable feature of built-in redundancy.
https://www.greenlight.guru/blog/managing-design-controls-on-spreadsheets

9. Post market surveillance

9.1 The Vigilance System

Reference in the text: Sections 6.3.8, 6.3.14.2, 6.3.15

The MDCG has updated its published guidance on the vigilance system for CE marked medical devices. That is, the system for reporting adverse incidents to the relevant authorities. It also covers routine periodic reports that are required under MDR 17/745.
https://health.ec.europa.eu/document/download/dbd0d748-d646-4274-afaa-399952809389_en?filename=mdcg_2024-1_en.pdf (January 2024).

A template form (compliant with the EU MDR) for the reporting serious adverse incidents can be downloaded from:
https://info.advisera.com/13485academy/free-download/manufacturer-incident-report-for-serious-incidents-and-incidents/ (February 2024)

10. Device labelling and registration

10.1 EUDAMED

Reference in the text: Section 6.3.14.2

The development of the EUDAMED database continues to grind on 7 years after the publication of EU MDR regulations that made it a key requirement. There is now (July 2024) a new draft for the roll out of EUDAMED that pushes the final implementation date back to 2027.

https://health.ec.europa.eu/document/download/04ce2012-97df-4dd0-8a39-d4f6993b9e16_en?filename=md_eudamed_roadmap_en.pdf

11. Medical device regulatory updates

11.1 EU medical device regulations

11.1.1 General issues and industry response

Reference in the text: Section 6.3

The following MedTech Europe "position paper" is undated but assumed to be published in October or November 2023.
https://www.medtecheurope.org/wp-content/uploads/2023/11/medtech-europe_future-of-medical-technology-regulations_position-paper_2023.pdf

The report is critical of the EU regulatory system and identifies what it perceives as several fundamental problems associated with lack of transparency and inconsistent application of the rules by Notified Bodies. Several solutions to the perceived problems are proposed.

Commenting in support of the MedTech Europe position, other interested parties have proposed that the regulatory scientists model the effects of proposed changes in legislation prior to their introduction, in a similar way to how the FDA runs pilot schemes [Johner Institute Journal, 40/23, 28 November 2023].

11.1.2 Transition arrangements from MDD to MDR

Reference in the text: Section 6.3.1.1

Confirmation of the new transition deadlines, plus more detail on the background and rationale can be found here:

https://advisera.com/articles/deadlines-for-medical-device-manufacturers-to-transition-from-mdd-to-mdr/

11.2 UK medical device regulations

Reference in the text: Section 6.4

11.2.1 MHRA guidance

The MHRA is due to update its guidance on *Managing Medical Devices* in the first half of 2024. The revision will be based on the 2022 consultation process but is bound to continue to refer to the current 2002 UK Medical Device Regulations. The existing guidance can be found here: https://www.gov.uk/government/publications/managing-medical-devices

New “All new” UK medical device regulations are not now expected until July 2025.

11.2.2 Draft Statutory Instrument to amend the post market surveillance (PMS) requirements of the UK Medical Devices Regulations 2002.

Reference in the text: Section 9.4.1

In July 2023 the UK government published a *draft* statutory instrument on the World Health Organisation website to amend the Medical Devices Regulations 2022. This draft legislation is limited, aiming (only) to insert new post-market surveillance (PMS) requirements for medical devices placed on the market in Great Britain (GB). If passed by Parliament, it is expected that this legislation will come into force in mid-2024.

The publication of this draft statutory instrument follows the 2021 MHRA consultation on the future regulation of medical devices in the UK and is part of the much wider revamp of the UK's medical device regulatory framework following Brexit. It should there be seen as an interim measure pending the complete replacement of the UK MDR 2002 in 2025. Medical devices placed on the market in Northern Ireland will continue to be subject to the EU regulatory framework under the Northern Ireland Protocol.

The requirements in the proposed UK PMS regulations closely resemble those already established in the EU Medical Device Regulation 2017/745, but there are some differences in the definition of some terms as well as associated requirements. The main differences - and the implications for medical device manufacturers - are summarised in the web page below: https://www.taylorwessing.com/en/insights-and-events/insights/2023/09/updated-post-market-surveillance-rules-for-medical-devices-in-the-uk (accessed 21/02/2024)

The *existing* arrangements (as of February 2024) for post-market surveillance of medical devices placed on the UK market are summarised in the guidance below: https://www.digitalregulations.innovation.nhs.uk/developers-guidance/all-developers-guidance/post-market-surveillance-medical-devices/ (accessed 21/02/2024)

11.2.3 Definition of Health Institution

Reference in the text: Sections 6.3.11, 6.4.6.

One of the things eagerly awaited by clinical scientists and engineers working in the NHS is what the above revised MHRA guidance has to say about the so-called health institution exemption (HIE). Prompted by the publication of MDCG guidance on the HIE under Article 5.5 of EU MDR 17/745 [see link below], the question of definition of a “health institution” has been recently debated in IPEM forums.
https://health.ec.europa.eu/system/files/2023-01/mdcg_2023-1_en.pdf (January 2023).

11.3 US medical device regulations

11.3.1 Recognised consensus standards

Reference in the text: Sections 5.1, 6.5.7

The FDA has pulled together all the information about recognised consensus standards into one database, which is called "List 61". It includes new standards and new versions of recognized standards, as well as revisions to some standards' extent of recognition.
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/results.cfm

A significant new addition is *ANSI/AAMI SW96:2023 Standard for Medical Device Security – Security Risk Management for Device Manufacturers,* which focuses on medical device security (see Section 6.5.8.11 and Chapter 8 of the book). The standard addresses cybersecurity risks, aligns with international risk management standards, and provides guidance for manufacturers in managing cybersecurity risks in device design.

11.3.2 Risk assessment related to device usability

Reference in the text: Sections 6.5.8.10

Usability engineering (UE) – or human factors engineering (HFE) as the FDA calls it – is the process and identifying and mitigating identified risks associated with usability. The subject is comprehensively covered in the book, but the regulatory agencies are constantly refining their approaches.

The latest draft guidance from the FDA concerns what it calls *use-related risk analysis* (URRA) and is primarily aimed at developers of drugs, biological products and combinational products. The latter, of course, include medical devices but the general principles contained in the draft guidance can also be applied to pure medical devices.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/purpose-and-content-use-related-risk-analyses-drugs-biological-products-and-combination-products

The draft guidance does not refer specifically to the main international standard (IEC 62366) but does refer to its own previous (2016) guidance on *Applying Human Factors and Usability Engineering to Medical Devices*.

The URRA essentially a tool to help ensure that all the possible risks associated with usability are identified early in the design process. There are clearly some gaps in the draft guidance, most of which have been identified by Moon and Matthew in their recent review:

https://www.meddeviceonline.com/doc/fda-issues-draft-guidance-on-use-related-risk-analysis-urra-0001

The closing date for public comments ended on 9 September 2024, so a final version is expected sometime in 2025. In the meantime, medical device manufactures in the US are advised to continue with their existing procedures.

11.4 An overview of the EU, UK, and US medical device markets

Reference in the text: Section 6.2

The following article offers advice to medical device manufacturers on which medical device market to enter first (EU or US).
https://www.meddeviceonline.com/doc/the-u-s-eu-or-u-k-which-medical-device-market-should-i-enter-first-0001 (published 6 November 2023)

11.5 Regulation of SaMD in Australia

Reference in the text: Section 6.3.4.6.

Passing reference was made in the book to Australian SaMD regulation in the context of clinical decision support (CDS) software. However, the regulations produced by the Therapeutic Goods Administration (TGA) cover the whole range of medical software, including SaMD.
https://www.meddeviceonline.com/doc/understanding-australia-s-regulatory-framework-for-samd-0001

12. Product liability law

12.1 EU Product Liability Law

Reference in the text: Sections 7.2, 7.2.2.

Latest updates are generally linked to this article about how EU product liability law affects medical device manufacturers:
https://www.johner-institut.de/blog/regulatory-affairs/produkthaftung/

The new EU Product Liability Directive (2024/2583) was published in the EU Official Journal on 18 November 2024. It will replace Directive 85/374/EEC. As a Directive, member states have 2 years to transpose the legislation into national law. The new laws will therefore only apply to products placed on the market or put into service after that transition period expires (i.e. November 2026). Until then, the existing PLD will continue to apply.

In brief, the new Directive will make it easier and simpler for a claimant to gain compensation for damages due to a faulty product, by expanding the definitions of key terms (‘defective’, ‘damage’ and ‘product’) and extending the range of individuals in the supply chain who may be held liable.

Embedded and standalone software (including AI software) is specifically included in the new definition of a product, the only exception being free and open-source software.

For more information, see:

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L_202402853

https://www.twobirds.com/en/insights/2024/germany/update-reform-der-produkthaftung-beschlossen

https://www.cov.com/en/news-and-insights/insights/2024/10/what-can-you-expect-from-the-new-product-liability-directive

12.2 US Products Liability Law

Reference in the text: Section 7.3.2

Notwithstanding the legal argument about whether medical software constitutes a "product", there is a legal principle (applicable in most US states) known as the "learned intermediary doctrine" that may insulate the manufacturer of medical products (drugs or devices) from product liability claims.

In brief, provided that the manufacturer supplied adequate accompanying written information on the drug/device (including warnings about any risks) to the treating physician (i.e., the "learned intermediary"), any *subsequent* treatment decisions made by the physician "breaks the line of causation" [of harm] between the manufacturer and the patient. In several specific cases (usually involving potentially harmful drug side effects that were not explained to the patient by the prescribing doctor) US courts have generally held that the "buck stops with the physician".
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6173549/

Clearly, there must be defined 'supply chain' ending with a specific prescribing decision by a learned medical professional. In the context of medical devices, the doctrine would probably only apply to small treatment devices prescribed for individual use (CPAP[5] machine, 24hr ECG monitor, etc.). It is unclear if or how this doctrine might apply to 'mass-use' diagnostic or therapeutic medical devices managed by central hospital departments, such as CT scanners or radiotherapy machines.

Note: the *learned intermediary doctrine* is referred to in the 2021 WHO report on *Ethics and Governance of Artificial Intelligence for Health*, under the heading "Are machine-learning algorithms products"?
https://www.who.int/publications/i/item/9789240029200

See also Section 6.12 above, relating specifically to AI-enabled devices.

[5] Continuous positive airway pressure. A CPAP machine is used for the treatment of sleep apnoea.

13. Programming languages and tools

13.1 Microsoft Excel™

Reference in the text: Section 3.3.3

It is now possible to write Python code directly from within Excel, which has several potential benefits for data scientists:
https://www.kdnuggets.com/python-in-excel-this-will-change-data-science-forever
(written 18 September 2023, accessed 22 February 2024)

Given that Microsoft's LLM can now be accessed from within Microsoft 365 apps (including Excel), this provides a Python code generating tool that can potentially be used to produce a range of AI-based applications.
https://blogs.microsoft.com/blog/2023/03/16/introducing-microsoft-365-copilot-your-copilot-for-work/

However, it should be noted that this Python-in-Excel facility is currently only available when using web-based Excel (i.e. Microsoft 365), not from the locally installed Microsoft Office desktop app that most clinical scientists use.

14. Standards

14.1 Harmonisation process

Reference in the text: Section 6.3.3

The EC has recently (May 2024) published a further amendment to its original (2021) standardisation request (to CEN/CENELEC) that pushes most of the adoption deadlines from May 2024 back to May 2028!

https://ec.europa.eu/transparency/documents-register/detail?ref=C(2024)3371&lang=en

This has caused consternation in some quarters and a public post on LinkedIn prompted an official response from the EC:

https://www.linkedin.com/posts/christian-rosenzweig-150810134_register-of-commission-documents-activity-7209821520267788290-l-HU/

The "bottom line" is that some standards that are key to medical device software development (e.g. IEC 62304, IEC 62366-1, IEC 81001-5-1) will probably not now be harmonised until 2028, even though they must be followed as representing the current state of the art. Note that ISO 14971 and ISO 13485 are already harmonised with respect to MDR 17.

END OF TEXT

Book reference list

This is a complete set of book references, with hyperlinks where appropriate. A few links given in the book no longer work due to the website in question being replaced or removed by the host organisation. Some links given below therefore replace the corresponding URLs given in the book. The links were checked and confirmed current as of 2 February 2024.

Note: For FDA and UK Government documents, the date given is either the date originally published, *or* the date last reviewed and declared "still current", whichever is the most recent.

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Chapter 6

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Chapter 7

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ENDS

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Section 3.2: Software Bill of Materials (SBOM)
Section 3.7: Clinical information systems (CIS)
Section 6.1.1, 6.1.5, 6.1.6: EU AI Act related.
Section 6.13: AI ethics etc
Section 6.14. The UK's "AI Airlock"
Section 10: EUDAMED delays
Section 14: Delays in the standards harmonisation process

Version 2.6 changes (c.f. v2.5)

Section 6.7.4: Regulatory issues and controversies surrounding LLMs used in healthcare
Section 6.13: New references added

Version 2.7 changes (c.f. v2.6)

Section 12.1: New paragraph on the new (2024) EU Product Liability Directive.