REGULATORY FOCUS

Risk Management for Medical Devices—A Practical Approach

By Val Theisz

Imagine yourself in this situation: you just started working for a new company and you review the risk management file you need to include in the next device submission, which, by the way, is urgent.

You have a look at the Design History File (DHF). There is an FMEA you hope is up-to-date; a risk management plan that unfortunately lacks typical deliverables and a method for systematically tying together risks, hazards, requirements, controls, verification and validation data; a risk analysis spreadsheet whose conclusions do not seem to link to any other engineering documents; and an Essential Requirements checklist, more or less complete, somewhere else.

But nothing seems to fit together, information in one document seems to duplicate or contradict information in other documents and, frankly, it feels like you cannot see the forest for the trees. Does this sound familiar?

Should you just "chuck in" whatever you find in the DHF that seems relevant to the risk management section of the submission and deal with the inevitable questions from the regulatory authority later, or worse, allow significant safety trends go unnoticed and miss implementation of necessary mitigation measures?

Or, having recognized that the risk management process itself is deficient, should you bite the bullet and address this more fundamental issue first, but risk delaying the submission in exchange for mid- and long-term benefits? If you decide on the latter course and if you have buy-in from other key stakeholders in your company, this article is for you.

Where to Start?

The ISO 14971 standard defines the process of managing risk throughout the lifecycle of a medical device, from initial identification of hazards associated with the device to assessment and control of risks to monitoring of the effectiveness of the control measures.

The process begins with identifying the hazards to patients and operators. Reading through ISO 14971:2007, especially Section E.2, Examples of hazards, it becomes readily apparent the list of hazards in Table E.1 looks very similar to the Essential Requirements or Principles of Safety and Effectiveness defined in regulations across three markets (the EU, Canada and Australia), the Global Harmonization Task Force N41 guidance document[1] and, to some degree, FDA list for substantial equivalence comparison for a 510(k) submission.[2]

It makes sense, then, to use the Essential Requirements checklist for the initial, top-down risk analysis, which must include identification of known or foreseeable hazards (ISO 14971 Section 4.3), to cover the "generic" hazards related to:

- chemical, physical and biological properties: toxicity, flammability, contamination and compatibility with substances and other materials
- infection and microbial contamination: use of tissues of animal origins and sterility
- device construction and environmental properties: physical features, electromagnetic compatibility and other environmental conditions, reciprocal interference with other devices, aging of materials and flammability
- device's measuring function: accuracy and stability
- radiation: intended and unintended
- electronic programmable systems and software: repeatability, reliability and performance
- device's energy source: electrical, mechanical and thermal risks
- device's energy supplies or substances: accuracy and stability
- device's controls and indicators: clarity to patient and user
- instructions for use: completeness, accuracy, clarity and suitability

The risks from most generic hazards listed above can be mitigated by a design that complies with published standards such as the IEC 60601 series, the ISO 10993 series or other applicable horizontal or vertical standards (ISO 14971 sections 6.2, 6.3 and 6.4)[3], and by robust manufacturing and postmarketing controls defined in ISO 13485 and relevant regulatory guidelines (ISO 14971, Section 9).

However, as standards cannot always fully replicate real-life situations, compliance with their requirements will only ensure a minimum level of safety. For a particular medical device, in addition to the generic hazards listed above, there are specific hazards related to its intended use that need to be considered.

In order to identify potential hazards to patients and users from the use of a specific type of device, a preliminary analysis of all product-specific clinical hazards should be performed. The risk evaluation and risk acceptability level should reflect the current standards, taking into account levels of risk for similar devices already in use and the latest data published in the clinical literature.

This means identifying from the literature review the specific hazards associated with the device and the percentage of patients affected or likely to be affected. Each hazard is assigned a probability of occurrence and a severity level, depending upon the possible consequences to the patient and user.

The combination of severity and probability of occurrence determines the estimated risk class for that hazard. Any hazard not meeting the acceptability targets will require control measures that must be included in the design inputs.

For instance, known clinical hazards specific to ventricular assist devices (VADs) that are attributable to the device are:

- cardiac failure
- infection
- central nervous system event
- organ failure
- respiratory failure
- bleeding
- device failure
- renal failure
- hepatic failure
- malignancy

- arterial embolism
- cardiac tamponade
- post-explant failure to recover[4]

These hazards arise due to the inherent risk of medical treatment using VADs, from device failures (or malfunctions) and from device use. A VAD manufacturer will use relevant information published in medical journals to set acceptability targets for patient survival rates and incidences of occurrence of VAD-specific clinical hazards, including device malfunction or failure.

As most medical devices will experience some sort of device malfunction or failure during their lifetime, manufacturers must monitor how their devices perform compared to what is considered acceptable according to the state-of-the-art. This information can usually be found in the medical literature and should be used as the benchmark for the acceptability targets set in the risk management plan.

As new or improved technologies become available, expectations for device safety and effectiveness performance increase and the benchmark for acceptable incidence of adverse events becomes more stringent.[5]

Considerations for Risk Control

Design compliance with the requirements of applicable product standards is generally considered an acceptable control measure for generic risks (electrical, mechanical, chemical, etc.) in the premarket phase of the product lifecycle, but additional measures may be required depending upon the risk definitions (severity and likelihood) and acceptability criteria. The design must also address all known or foreseeable product-specific clinical hazards, including those that are the result of device failure or malfunction.

The risk control measures adopted by the manufacturer should be, in order of preference: intrinsically safe design, protective measures (barriers, alarms) and warnings/contraindications (ISO 14971 Section 6).

For example, a life-sustaining VAD with an external controller relies on electrical power for its function and, as such, must have built-in power redundancy. A typical solution is to have two power sources at any one time, such as a main and reserve battery or a main power supply and a reserve battery.

The removal of one power source must automatically switch the controller to the other power source without interruption. The controller itself must function reliably; therefore, it should also have built-in redundancy, so if the main firmware fails, control is transferred automatically to the slave firmware. The slave should have a different architecture and run on a different type of microprocessor than the main firmware to mitigate the risk of same type of failure's happening twice.

Controller connectors for the power cables, the percutaneous lead and the communication lead should have designs (shapes) that are incompatible with each other to avoid incorrect connection. Appropriate alarms must be built into the controller to indicate battery charge level and any abnormal function, such as pump operating parameters outside the set range.

If, for any reason, the controller must be changed, a prominent warning in the instructions for use must state this can only be done a by a trained caregiver and the patient should not attempt to do this alone.

The applicable generic hazards and the specific clinical hazards should be identified up front in the design and development process, at the planning stage of the product realization phase (ISO 13485 section 7.1). The product requirements defined as part of the design input (ISO 13485 section 7.3.2) should include the risk control measures agreed upon as a result of the preliminary risk analysis, as well as subsequent controls derived from other activities throughout the lifecycle.

In the case of devices already on the market, a risk management file may need to be compiled retrospectively. Implementation of an ISO 14971-compliant risk management process is mandatory for manufacturers seeking compliance with the third edition of IEC 60601-1 (IEC 60601-1 Third Edition 2005-12 subclause 4.2).

Most manufacturers have a spreadsheet or a database, depending upon device complexity, to track each individual design input requirement throughout the entire design and

development process. It is important to make sure the requirements are complete, unambiguous and not duplicated or in conflict with each other.

Once the detailed product design is near completion, various in-depth risk analysis techniques, such as Failure Mode and Effects/ Criticality Analysis (FMEA/FMECA), Fault Tree Analysis (FTA) and Event Analysis, can be used to address hazards caused by device malfunction, as well as hazards resulting from interactions between user and device, to select appropriate control measures, which are then fed back into the design process. Conventional reliability analyses used for the detection of device failures and malfunctions must be complemented by robust usability analyses to minimize the risk from device use errors.

Studies cited by FDA indicate "the frequency and consequence of hazards resulting from medical device use might far exceed those arising from device failures".[6] According to a report by the ECRI Institute, "General estimates suggest that up to 90% of all errors in medicine are caused by human error [...], with human error in medical device accidents accounting for 50-70% of all device related accidents."[7]

The importance of usability was also highlighted in the 2007 amendment of the European *Medical Devices Directive*, which added a requirement for "reducing, as far as possible, the risk of use error due to the ergonomic features of the device and the environment in which the device is intended to be used" (Directive 2007/47/EC, ANNEX II.1). Manufacturers can refer to published standards that specify requirements for a process to analyze, design, verify and validate usability as it relates to the safety of medical devices in general (IEC 62366) or electrical medical devices in particular (IEC 60601-1-6).

An increasing number of medical devices use software. A 2009 report by the ECRI Institute identifies computerized equipment and systems as one of the top 10 medical technology hazards.[8]

Software, either standalone or contained in medical devices, must be analyzed for risk as well. The control measures for hazard mitigation and the level of documentation required for a regulatory submission will be determined by the level of concern (LoC), i.e., the estimate of the severity of injury to a patient or user as a result of malfunction or failure.[9]

Back to the VAD example, the controller firmware and any customized software used for setting and viewing of VAD programmable system parameters, for monitoring VAD performance and for viewing and downloading patient and implant data must be analyzed to determine which system functionalities these software devices are responsible for and the LoC associated with each software device.

For instance, setting an inappropriate pump speed may lead to hemorrhage and death. There is a major LoC associated with software within the controller responsible to ensure that only values within a valid range are applied. Similarly, software responsible for displaying VAD parameters and alarm conditions has a major LoC, because a malfunction may lead to a failure to detect problems with the power supply or pump settings, which in turn may lead to a serious adverse event or death.

Software development must follow a defined lifecycle process, with documented software requirements and design specifications, software risk analysis, configuration management, verification and validation. The IEC 60601-1-4 collateral standard for programmable electrical medical systems, recently replaced by clause 14 of IEC 60601-1 3rd Edition, and the IEC 62304 standard for medical device software lifecycle processes are the current benchmarks for ensuring compliance with regulatory requirements.

In the design implementation phase, FMEA/FMECA and other techniques can be used to analyze processes and determine the risks introduced in manufacturing, during *in vitro* testing and by users of the product.

Design verification must ensure all risk control measures have been implemented in the final design. Design validation, which may use a validation study or a clinical study for higher-risk or novel devices, should establish whether the risk control measures as implemented are effective, i.e., whether the residual risks are acceptable.

A risk-benefit analysis will determine whether the residual risk, if any, is acceptable, once all practicable measures to reduce the risk have been applied. Overall, the expected benefits to the patient must outweigh the risks.

According to ISO 14971, "The decision as to whether risks are outweighed by benefits is essentially a matter of judgment by experienced and knowledgeable individuals. An important consideration in the acceptability of a residual risk is whether an anticipated

clinical benefit can be achieved through the use of alternative design solutions or therapeutic options that avoid exposure to that risk or reduce the overall risk."

A recently published FDA guidance sheds some light on the factors agency reviewers take into consideration when making risk-benefit determinations.[10] These factors include:

- extent of the probable benefits: type of benefits; magnitude of benefits; probability of the patient's experiencing one or more benefits; duration of effect of the benefit(s)
- extent of the probable risks and harm: severity, number and rates of harmful events associated with the use of the device (device-related serious and non-serious adverse events and procedure-related complications); probability of a harmful event; duration of harmful events; risk from false-positive or false-negative results for diagnostics
- uncertainty, e.g., poor design/conduct of clinical trials or inadequate analysis of data
- characterization of the disease
- patient tolerance for risk and perspective on benefit
- availability of alternative treatments or diagnostics
- novel technology addressing unmet medical need

With all their intrinsic risks, VADs have been shown to prolong life and improve quality of life by providing circulatory support in patients suffering from heart failure who are not responding to conventional medical therapy.

The determination of whether, for a particular VAD, the benefits outweigh the risks must take into consideration a thorough analysis of field data such as patient survival rates and adverse events collected from well-controlled clinical trials, comparison of risks and reliability from field data against baselines defined in the preliminary risk analysis and evidence that all risk controls were implemented.

Ongoing Maintenance in Postmarket Phase

When assessing product and process changes for continued regulatory compliance, the regulatory professional should analyze which requirements are affected by the change, taking into consideration interdependencies across design input, design output and verification and validation activities, as well as changes in form, fit and function at the system and sub-system level and how they affect the overall configuration of the medical device. This analysis will often determine whether a change is "minor" or "major" and whether it requires notification of or preapproval by regulatory authorities.

Using the VAD example, before a change in supplier is approved, the vascular grafts may require an assessment against dimensional requirements, biocompatibility of materials, protection against transmissible spongiform encephalopathy (TSE) if impregnated with gelatin and quality assurance systems of the supplier including sterilization process validation. Before a change in indication for use is approved, for instance, from adult to pediatric use, a complete review of all product requirements might be required, from pump parameters to software and dimensional requirements, and additional clinical studies may be required for final validation.

Vigilance and postmarket surveillance systems must ensure information gained from collection of postmarket data is fed back into the risk management system and additional control measures are adopted as necessary. As with pharmaceutical products, it is worth monitoring trends in device adverse events and analyzing how the manufacturer's products compare with competitors' products, and to take early action, if needed, before the regulator or a newspaper asks, "Why do your products have a higher incidence of adverse events compared to similar products currently on the market?"

Conclusion

No medical device is risk free, but risks can be managed. Applying a rigorous and systematic approach, manufacturers can determine the risks are associated with the use of their medical devices and minimize them using risk control measures.

A well-structured and well-maintained risk management system should be fully integrated in the medical device lifecycle to ensure risks associated with the use of the device remain as low as practicable. The role of the regulatory professional is to "connect the dots" and provide lifecycle oversight for the risk management process, as he or she is the

one chasing up specific deliverables from others when submissions are required or when things go wrong.

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