A method for quantitative estimate of risk probability in use risk assessment

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Abstract

Risks analysis requires that foreseeable risks related to usage of medical products are assessed and that mitigations are in place, so that use related hazards are as low as reasonably possible. It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. International standards (notably ISO14971-2012) suggest that “foreseeable sequences of events that can produce hazardous situations and harm” should be considered, since: “a hazard cannot result in harm until […] a sequence of events […] lead to a hazardous situation”. Sequence of events is probabilistic, and should be described considering the probability of hazards leading to hazardous situations ($P_1$), combing with the probability of hazardous situations leading to harms ($P_2$). $P_1$ and $P_2$ are essential in that their joint probability defines the likelihood of occurrence of harm, which is defined as, the “physical injury or damage to the health of people”. Whilst the international standards suggest that use errors have to be considered, it does not clarify how to connect the probability of hazardous situations occurring ($P_1$) and the probability of hazardous situation leading to harm ($P_2$) with the probability that users may commit those errors. The present work proposes a method which enables quantitative estimations of use errors and clearly relates them to $P_1$ and $P_2$ estimates.

Introduction

This work relates to the assessment of use related risk in the use of Medical Devices and Drug/Biologic-Device Combination Products. Medical devices can be broadly defined as apparatuses intended for the diagnosis or treatment of disease.

The regulatory definitions of drug/ biologic-device combination products can vary based on the region. For the purpose of this article, the US 21CFR part 3.2 (e) definition shall apply, which defines a combination product as:

(1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

The peculiarity of such devices used for the delivery of medicines resides in the fact that risks pertain two main components of the product: 1) the device(s), with any potential usability issues associated with their intended use or reasonably foreseeable misuse, and; 2) the medicinal product, whose administration entails potential risks associated with medication error, for example, administration by the wrong route, wrong dose or wrong rate (Vincent, 2010). When use errors occur, users are potentially exposed to hazards, hazardous situations, and, ultimately, to harm.

For Vincent (2010), the role of harm prevention is central to patient safety, and more prominent than prevention of error. Focusing on patient safety requires the manufacturers of devices and combination products to implement risk management processes.

Requirements for use related risk management

Medical device and medicinal product manufacturers are expected to perform risk analysis to identify known and foreseeable use related risks and to mitigate these risks to be within acceptable limits (WHO, 2016; EMA, 2015a, FDA, 2006).

The requirement to analyse and evaluate risks associated with use is broadly represented across regulation, harmonized/ recognized normative technical standards and a range of Health Authority guidance. The following section summarizes the current regulatory basis:

Under US Medical Device Quality System Regulation; risk analysis is a requirement of 21CFR820.30 (g) Design Validation (also applicable to combination products in accordance with 21CFR part 4):

“...Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under
quantitative estimate of risk probability

actual or simulated use conditions. Design validation shall include software validation and risk analysis, where appropriate....”

In the European Union (EU), the Essential Requirements of the European Medical Device Directive herein referred to as the MDD (Council Directive 93/42/EEC of 14 June 1993, incl. 2007/47/EC), states that the devices must be designed and manufactured in such a way as:

“...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 (design for patient safety)”.

The requirement for use related risk analysis is also integral to two Medical Device normative standards as harmonized to the EU MDD, and recognized as Medical Device consensus standards by the US Food and Drug Administration (FDA), namely:

- IEC 62366-1:2015 Medical Devices - Part 1: Application of Usability Engineering to Medical Devices, is recognized by the US FDA, currently an earlier version of the standard EN 62366:2008 is harmonized to the EU MDD.

- EN ISO 14971:2012 Medical devices - Application of risk management to medical devices, is a harmonized standard to the EU MDD, currently the preceding version of the standard ISO 14971:2007 (R) 2010 is a recognized consensus standard by the US FDA.

Finally, the importance of use related risk management as part of the Human Factors (HF) process for the development of medical devices and drug-device combination products is also underscored by a wealth of guidance from the US Food and Drug Administration (FDA 2016a, 2016b, 2016c), European Medicines Agency (EMA 2015b), the UK’s Medical and Healthcare Products Regulatory Agency (MHRA, 2016), and importantly the International Conference of Harmonization of technical requirements for registration of pharmaceuticals for Human use guidance: ICH-Q9 (EMA, 2015a; FDA 2006).

**Integration of Risk Management into the HF Engineering process**

Use related risk management is integral to the HF Engineering/ Usability Engineering (UE) process as use-related error may have significant impact on patient safety and result in harm, including physical injury or adverse health consequences.

The HF/ UE process is intended to identify and minimize use errors and thereby reduce use associated risks (IEC 62366-1:2015).

The HF/ UE process requires that hazards related to use should be identified and addressed during the device development, including:

- Identifying user interface characteristics related to safety.
Identifying known and foreseeable hazards and hazardous situations associated with use.

Defining a user interface that includes necessary risk control measures.

Performing formative and summative usability evaluation to determine the use safety and effectiveness of the user interface.

Informing the overall risk assessment and the evaluation of use related residual risk.

Thus, the use related risk analysis plays an essential role in implementing strategies to improve patient safety by identifying and reducing hazards and preventing harm.

The notion of harm plays a central role in patient safety and in the risk management process. Vincent (2010) argues that harm is what patients most care about, because not all harms are the result of errors, and because not all errors necessarily lead to harms. Therefore accurately understanding which errors are most likely to lead to harm is a key concept in identifying so called “safety-critical” tasks and prioritizing risk mitigations.

**Risk management process**

A risk management process (RMP) is intended to systematically apply management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk (EN ISO14971:2012).

Specifically, the normative standard requires that throughout the lifecycle process of device development and commercialization, a RMP is initiated and maintained, and comprises the following phases (EN ISO14971:2012; Claycamp, 2015):

- planning the RM activities;
- risk analysis, including defining the intended use of the device, systematic identification of hazards, the consequences of the hazards, and the estimation of the associated risks;
- risk evaluation, consisting of an assessment of the risks and criteria to determine risks acceptability and/or controls;
- risk control, that is, actions aimed at mitigating potential risks assessed as requiring further mitigation. Residual risks present after the execution of risk control actions are assessed in a risk to benefits analysis performed as part of an overall product risk evaluation;
- output review, the results (or output) of the RMP are reviewed and communicated as appropriate;
- risk must be systematically monitored throughout the product lifecycle on the basis of production and post-production information, for example, post-market Complaints and Adverse Event reports.

For the purposes of the present work the phases entailing the risk analysis and the risk evaluation phases (and to some extent the post-market phase) are of particular concern.
Characterization of harm and risk

It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm (ICH, 2005; ISO/IEC Guide 51; EN ISO 14971:2012). Severity ($S_{\text{harm}}$) is a “measure of the possible consequences of a hazard” (EN ISO14971:2012). In the specific case of combination products, evaluating such a measure requires a thorough clinical assessment, since specific clinical knowledge is usually necessary to determine the potential consequences of patient harm that could result from the device or medicinal product.

For instance, the impact of harm in patients can vary from being negligible (e.g. delayed dose delivery with negligible clinical impact), to serious (e.g. infection or disease progression with clinical consequences requiring medical intervention), to catastrophic or fatal (e.g. overdose leading to death).

Along with the dimension of severity, the likelihood (or probability) of harm occurring characterizes the level of risk. Probability of occurrence of harm ($P_{\text{harm}}$) is defined as being given by $P_{\text{harm}} = P_1 \times P_2$ (EN ISO14791: 2012), where: $P_1$ is the probability of being exposed to a hazardous situation, and $P_2$ is the probability of the hazardous situation leading to harm.

Typically, an evaluation of risk is represented in the form of a matrix, where both severity and probability are expressed in terms of qualitative category and/or a numerical (categorical) score (EN ISO14791: 2012). An example is illustrated in Table 1.

<table>
<thead>
<tr>
<th>Severity ($S_{\text{harm}}$)</th>
<th>2 (Negligible)</th>
<th>4 (Moderate)</th>
<th>6 (Severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability ($P_{\text{harm}}$)</td>
<td>2 (Remote)</td>
<td>Risk #a</td>
<td>Risk #b</td>
</tr>
<tr>
<td></td>
<td>4 (Occasional)</td>
<td>Risk #c</td>
<td>Risk #d</td>
</tr>
<tr>
<td></td>
<td>6 (Frequent)</td>
<td>Risk #e</td>
<td>Risk #f</td>
</tr>
</tbody>
</table>

When probability and severity scores are considered together (typically, they are multiplied), the resulting value represents a summative measure of the risk and can be evaluated against pre-defined criteria of acceptability. For example, it can be defined that all risks having “negligible” severity and “remote” probability (hence, with a resulting risk number of “4” (i.e. $S_{\text{harm}} \times P_{\text{harm}} = 4$) can be considered acceptable; whereas all other risks may be deemed unacceptable and require further mitigation.
Defining the qualitative categories and/or numerical scores is the responsibility of the manufacturer, as well as acceptability threshold criteria and the appropriate rationale used to determine whether any specific risk number is considered acceptable or not.

To summarize, \( P_1 \) and \( P_2 \) are considered together to define \( P_{\text{harm}} \), which, in turn, combined with harm severity \( S_{\text{harm}} \) defines an overall estimate of the magnitude of a risk.

However, although it is established that the potential harm resulting from use errors should be considered in the overall RMP, it is not clear in EN ISO14971:2012 how to connect the probability that users may commit errors that have the potential to be harmful to the probability of hazardous situations occurring (\( P_1 \)) and the probability of hazardous situation leading to harm (\( P_2 \)).

Whilst this leaves some flexibility to interpret how to integrate the role of use error estimates into risk analysis, it does not provide a clear guidance on how to quantitatively relate the probability of use error to \( P_1 \) and \( P_2 \).

The present work tackles this problem in that it proposes a method which enables quantitative estimations of use errors and clearly relates them to the estimations of \( P_1 \) and \( P_2 \).

**Quantitative estimation of probability of harm**

The construct validity of risk analysis at estimating the true risk profile is determined by the accuracy of the harm severity and probability of harm occurrence estimates. Severity of harm is defined based on clinical understanding and can be supported by clinical data. However, the probability of the harm occurring is the result of a series of circumstances.

A key challenge in assigning probability scores are that by definition, probability is being estimated, and stakeholders may vary in their estimation of the probability (ICH, 2005; Onofrio, Piccagli & Segato, 2015).

Modelling the probability of occurrence of harm therefore requires an assessment of the constituent circumstances that enable a harmful event to occur. The widely accepted “Swiss cheese” model (SCM) of accident causation (Reason, 1990; Reason, 1997) provides a general framework for analysing failures in complex systems and has become the dominant model for understanding system failures in error causation (Perneger, 2005).

SCM represents the path to a failure as a series of active failures and latent conditions represented as holes in “Swiss cheese”. The metaphor of swiss cheese is represented by slices of cheese with holes stacked in a row. For harm to occur, holes must align, thereby providing a pathway for the failure to occur. The SCM model is widely used; however one of the criticisms directed at SCM is its lack of specificity in how it is actually used in practice (Reason et al., 2006).
Our proposed probability estimation method is based on the SCM principle, where the events that may lead from use error to harm are represented as “the slices of cheese”, and “size of the hole in the cheese” represents the magnitude of the probability.

The basic two-level framework for applying this model is already described at a high level in EN ISO 14971, where it is defined that the probability of being exposed to a hazardous situation is designated with $P_1$ and the probability of the hazardous situation leading to harm is designated with $P_2$; the resultant probability of occurrence of harm is given by $P_1 \times P_2$.

The practical issue is that $P_1$ can be challenging to estimate as itself is the product of a cumulative combination of discrete probabilities. To improve $P_1$ estimation accuracy, our method introduces two constituents to derive $P_1$; i.e., $P_e$: The probability of an error occurring, and $P_0$: The probability of the error causing the hazardous situation.

![Figure 7: Model of quantitative estimation of occurrence of harm resulting from a use error](image)

Therefore, the overall probability of harm occurring as a result of an error can be represented as:

$$P_{harm} = (P_e \times P_0) \times P_2$$
P_e: Probability of an error occurring is often related to the usability of the user interface (e.g. the probability of a user not checking an expiry date of a medicine prior to use). The likelihood of use errors occurring can be estimated throughout the HF process based on empirical HF studies, expert opinion, known issues, etc.

P_0: Probability of error causing the hazardous situation. P_0 serves the purpose of modulating the impact of P_e in resulting in exposure to a specific hazardous situation. P_0 is necessary as not all use errors would result in exposure to hazardous situation (e.g. not checking an expiry date does not necessarily mean that the user would administer an expired product). Using ISO14791 definitions, P_0 may correspond to the probability of “hazard”, which (if a certain sequence of preceding events is triggered), may lead to the hazardous situation.

P_1: Probability of the hazardous situation occurring. In the proposed method, P_1 is the product of the probability of the error multiplied by the probability of use error causing the hazard (causing exposure to the hazardous situation), i.e. P_e x P_0.

P_2: Probability of the hazardous situation leading to harm (e.g. probability of administering an expired medicine leading to a specific harmful consequence, like an adverse clinical effect such as disease progression). The following examples illustrate two cases. The first refers to users not washing their hands prior to performing an injection and a remote likelihood of experiencing a systemic infection (i.e. probability of committing the error is high, but probability of harm is low). The second refers to users lifting an injection pen mid-injection; it is likely that this would lead to incomplete dose with a high probability of clinical impact (i.e. probability of committing error is high and probability of harm is consequently high).

<table>
<thead>
<tr>
<th>Definition</th>
<th>Probability</th>
<th>Cumulative probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>P_e</td>
<td>Use error: User fails to wash hands</td>
<td>0.5 (50%)</td>
</tr>
<tr>
<td>P_0</td>
<td>Hazard: Dirty hands touch the injection site</td>
<td>0.05 (5%)</td>
</tr>
<tr>
<td>P_1</td>
<td>Hazardous situation: Injection site is contaminated</td>
<td>-</td>
</tr>
<tr>
<td>P_2</td>
<td>Harm: Systemic infection</td>
<td>0.0001 (0.01%)</td>
</tr>
<tr>
<td>P_harm</td>
<td>Overall probability of occurrence of harm:</td>
<td>0.00000025 (0.00025%)</td>
</tr>
</tbody>
</table>
quantitative estimate of risk probability

Table 3. Example 2 – Quantitative estimates of $P_e$, $P_0$, $P_1$, and $P_0$, and how to derive $P_{harm}$

<table>
<thead>
<tr>
<th>Definition</th>
<th>Probability</th>
<th>Cumulative probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_e$</td>
<td>Probability of error occurring</td>
<td>Use error: User lifts device from injection site prior to injection completion</td>
</tr>
<tr>
<td>$P_0$</td>
<td>Probability of use error causing the hazardous situation</td>
<td>Hazard: device has not injected full volume</td>
</tr>
<tr>
<td>$P_1$</td>
<td>Probability of the hazardous situation occurring</td>
<td>Hazardous situation: Incomplete dose</td>
</tr>
<tr>
<td>$P_2$</td>
<td>Probability of the hazardous situation leading to harm</td>
<td>Harm: Significant disease progression due to lack of efficacy</td>
</tr>
<tr>
<td>$P_{harm}$</td>
<td>Overall probability of occurrence of harm:</td>
<td></td>
</tr>
</tbody>
</table>

The estimations reported in Table 2 & 3 are to be used as example only. However, in actual practice, estimates of $P_e$ can be based on data derived, for example, from literature, from formative or summative usability studies (of the device under investigation, or similar ones), clinical studies or market complaints from similar devices. Similarly, $P_0$ can be estimated from observations and data. Also, the involvement of a multidisciplinary team (e.g. clinical, technical scientists, potential end-users, and patients) may ensure that several and different viewpoints are considered in the assessment.

Estimates of $P_2$ may require the expert knowledge of clinical scientists and healthcare professionals, in order to more reliably establish the potential relations between hazardous situation and harm. Once $P_{harm}$ is derived, it is possible to translate this (quantitative) number into qualitative or numerical categories, based on pre-defined rationale, whereby, for example, specific $P_{harm}$ expressed as a percentage (e.g. 2%) may correspond to specific qualitative or numerical categories (e.g. “Frequent”, corresponding to “6”) in the risk matrix.

Evidence-based probability ratings

The present paper proposes a method to integrate quantitative estimates of use error into a use related risk assessment. It attempts to provide practical support to HF
practitioners to performing more accurate risk assessment where risks are linked to incidence of use error. There are advantages and disadvantages in the approach of deriving probability of harm based on constituent assessments.

The advantages would be, for instance: applicability and integration into existing approaches to risk analysis, as for example in Failure Mode and Risk Analysis (FMEA). The FMEA can be tailored to the use domain, and comprise individual probability assessments for \( P_e, P_0, P_1 \) & \( P_2 \) against the listed potential failure modes/ use errors identified for each specific task \( (P_e) \); hazards identified for each specific task \( (P_0) \); the consequential possible hazardous situations per task \( (P_1) \); and the corresponding harm related to each hazardous situation \( (P_2) \). But also, the method allows having greater confidence in the precision of probability estimation and the ability to adjust the individual constituent values throughout the risk management lifecycle when new information becomes available.

Another advantage is the increased traceability of the assessment outputs. As the method provides traceability of how quantitative data is reflected in the assessment. For example, if a HF summative study demonstrates a very high error rate than was previously assumed, \( P_e \) could be updated to demonstrate the rate was taken into account, but under certain circumstances this may not actually impact probability of harm estimation, because, as discussed above, high probability of error does not necessarily result in a high probability of occurrence of harm. This method also allows integrating real, post market data in the use related risk assessment. As a matter of fact, compared to traditional categorical estimations of probabilities, this method allows quickly integrating post-market (truly) quantitative data into the risk management review and updating as necessary.

The main foreseeable disadvantage of this method is related to the increased complexity and the likely time/ effort cost for the multiple individual probability assessments required per risk, especially if the number of tasks to be considered in the assessment is high. Nevertheless, this method proved to be easily applicable for home use drug delivery devices, where the overall number of tasks (and hence of risks) were within manageable limits.

**Potential wider application of the method**

Finally, the present method has discussed the estimation of harm probability as a consequence of a relatively ‘minimal’ and rudimentary series of conditions, as depicted in the examples of medical device use errors. However, the degree to which this method, or development of, could be easily applied in evaluating risk in more complex systems of a more multi-factorial and/or less predictable nature requires further investigation. The underlying premise that all failures in simple or complex systems result from a combination of latent condition pathways, failed defences and active failures (Reason, 1997) suggests that the step-wise estimation of the probability of failure at key stages defined in the present method could apply. However, it may be that to be effective and compatible in complex system risk analysis, each distinct stage of probability estimation (e.g. error, hazardous situation, harm) might require its own set of sub-probability modelling calculations to more accurately assess the summative impact of multiple factors; whenever this may be the case, factoring in pre-disposing
quantitative estimate of risk probability

factors such as latent conditions and personal characteristics (e.g. fatigue, cognitive load) could be challenging to allow straightforward integration.

Nevertheless, probability is an elementary factor in estimating the magnitude of risk and requires methods for estimation. Hence, even if applying this model to highly complex systems may present challenges, it could still provide a useful tool for quantitative probability estimation, and ultimately make risk analysis more accurate.

References


