SMi Systems

www.smisystems.co.uk

Risk Management

SMi Systems is developing analytics platforms for both the biomedical research and diagnostic markets. Here we discuss risk management and how we go about ensuring our products are as safe as possible.

Life sciences providers can develop products for both the research and diagnostic markets. Regulatory requirements for research use are significantly lower than those for diagnostics, but there are still requirements which must be met to achieve CE and/or UKCA marking and place these products into the hands of consumers.

Here we describe the differences between the regulatory considerations for research use only (RUO) products and those destined for *in vitro* diagnostics (IVD) use, and consider how risk management can be simultaneously applied.

RUO versus IVD

RUO products have a crucial role in facilitating fundamental research and are essential to the development of new therapies, diagnostic assays and tools. These specialised products include laboratory reagents and equipment and are exclusively designed for research in controlled laboratory environments. Manufacturers of RUO products clearly label them as RUO.

IVD products are devices and systems used to diagnose, treat, or prevent health conditions. They are used in the examination of biological samples like blood, saliva, or tissue. IVDs will often have a chemical or physical composition that is similar to an RUO, but their intended purpose is different and documented evidence is required to qualify a product as an IVD (**Box 1**).

> ***Regulation (EU) 2017/746*** *defines in vitro diagnostic medical devices as 'any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body'.*

Box 1 | Definition of an IVD according to EU regulations

Design and manufacture

Where the physical composition of RUO products is materially similar to those of their IVD counterpart, there is an opportunity for the legal manufacturer to combine elements of the design and manufacturing processes. This can have significant commercial advantages, but only if the respective standards can be applied efficiently. One area where design and manufacture processes can be combined is risk management.

Risk management

Risk management is the process of identifying, assessing and controlling outcomes which cannot be determined with absolute certainty.

For RUO products, the governing regulation depends upon the function of that product. If, it has powered mechanical moving parts, then the machinery directive (2006/42/EC) applies. This directive has ISO 12011:2010 as its harmonised standard for risk management.

In the EU, IVD devices are governed by Regulation (EU) 2017/746 which has ISO 14971:2019, application of risk management to medical devices, as its harmonised standard for risk management.

Whilst it's not mandated that a manufacturer must follow such harmonised standards, those who do so benefit from 'presumption of conformity' whereby adherence to the harmonised standards ensures that the resulting products are in line with the corresponding EU rules and can be sold in this market.

However, combining development activities to meet both these standards presents a set of challenges for risk management because the respective regulations have different harmonised standards (**Box 2**).

> *A harmonised standard is a technical standard developed and published by recognized standardization organizations, which ensures that products, services, or processes meet specific requirements and are consistent across different countries or regions. These standards are particularly important in facilitating trade and ensuring safety, quality, and interoperability of products and services.*

Box 2 | Definition of a harmonised standard.

Meeting the requirements of two risk management standards means choosing between one of three approaches:

(1) using and documenting separate risk management processes for RUO and IVD products.
(2) using both standards and performing risk management twice on each product.

(3) combining the requirements and documentation of each standard to ensure that one risk management process satisfies the requirements of both standards.

ISO 12100:2010 bears a lot of resemblance to earlier versions of ISO 14971, so the two standards share a common approach to risk analysis and control (**Fig 1**). One method of developing a risk management process that satisfies both standards is to work within the framework of the newer ISO 14971:2019, whilst applying only the requirements of ISO 12100:2010 to the RUO product and then supplementing those requirements with those of ISO 14971:2019 for the IVD product.

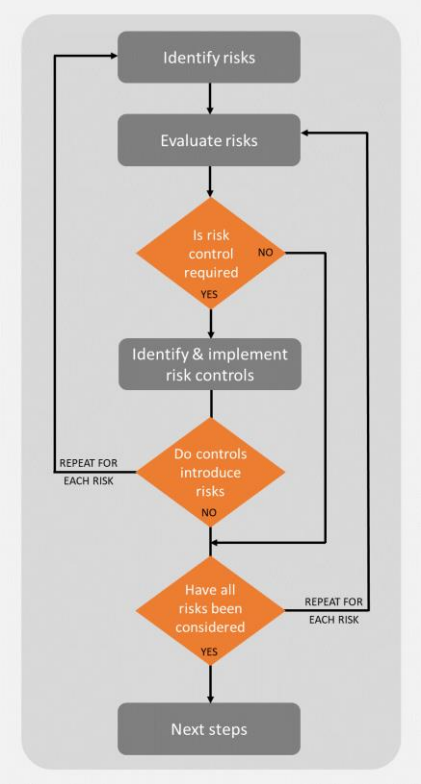

Fig 1 | Common elements of the risk management process

We asked Peter Sebelius[1], Founder and CEO of Medical Device HQ, who is a recognised expert in medical device risk management and a member of ISO/TC210, for his thoughts on this. He said " whilst I don't know of anyone who had done this, it seems like a valid approach."

Identifying risks

The first step in risk management, regardless of the standard being followed, is to identify the risks and the conditions under which the risks might occur.

For RUO products governed by ISO 12100:2010, risk identification focuses on establishing the limits of the machinery then considering reasonably foreseeable hazards that could occur within all phases of use. The standard includes examples of hazards and the accompanying Technical Report ISO/TR14121-2:2012 gives practical guidance on methods and tools to use.

[1] Peter Sebelius: https://www.linkedin.com/in/petersebelius

For IVD products governed by ISO 14971:2019 there is more focus on process and far fewer example hazards. However, the accompanying Technical Report ISO/TR24971:2020 has a much greater depth of practical guidance covering aspects such as identification of hazards and techniques to support risk analysis. It also includes a specific Annex on *in vitro* diagnostic devices.

Estimation of risk

Once risks have been identified, their likelihood of occurrence and severity must be evaluated. The combination of these two factors helps identify risks that should receive most attention when it comes to mitigation, though it should be noted, that EU IVD Regulation 2017/746 requires that *all* risks are reduced as far as possible without affecting the benefit risk ratio.

The approach to risk estimation is the same in both standards, but the method of estimation differs slightly (**Box 3**). From a practical perspective, the difference in definition is relatively small and documenting the resulting 'Probability of Occurrence' demonstrates compliance with each standard.

> ***ISO 12100:2010*** *defines the Probability of Occurrence of a Harm as a combination of (1) exposure to the potential hazard, (2) the occurrence of the hazardous event and (3) the possibility to limit or avoid the harm.*
>
> ***ISO 14971:2019*** *has no concept of the possibility to limit or avoid the harm and instead defines the Probability of Occurrence of a Harm as being a combination of (1) the probability of a hazardous situation occurring and (2) the possibility that such a situation will lead to a harm.*

Box 3 | Estimation methods. RUO products align with ISO 12100:210 and IVD's with ISO 14971:2019.

Limiting Risk

For each risk, mitigations (risk controls) are identified, and their effectiveness is determined. The approach to risk control is grouped into three categories (listed in order of preference below):

Inherently safe design – where product designs are changed to eliminate the original risk. For example, risk of mains electrocution can be eliminated if the product is designed to be powered by a low voltage battery instead.

Protective measure – where the risk cannot be eliminated by design, but it can be reduced. For example, a circular saw blade is intrinsic to the tool's function, but a guard can significantly reduce the chance of accidental contact.

Information for use – where design changes are not possible, instructions can enable the user to avoid risks. For example, foods often contain warnings such 'may contain nuts'. This warning does not reduce the nut content, nor does it protect the user from unintended contact.

Residual Risk

Both standards cover the handling of residual risk; that remaining after risk controls have been implemented. This must be communicated to the user, so they can make an informed decision whether to use the product.

ISO 14971:2019 has one additional step, the benefit-risk analysis (BRA). This requires manufacturers to weigh the residual risk of the product against the intended benefit that it delivers. Only IVD products for which the intended benefit outweighs the residual risk are acceptable. For example, chemotherapy uses powerful chemicals that can have serious side effects, but also provide a cure.

Post-production activities

The biggest difference between the two standards is in dealing with post-production risk.

ISO 12100:2010 requires the manufacturer to consider risk throughout the lifetime of the product, including installation, training, use, and servicing, but there is no requirement to formally collect and monitor post-production risk.

ISO 14971:2019 requires the manufacturer to have systems that actively collect and review information relevant to the medical device in both the production and post-production phases. This includes product details, publicly available information, and information about the state of the art such as similar competitor products.

Whilst post-production activities are not required for RUO products, in cases where RUO and IVD products are materially similar, the RUO product can be a valuable information source for post-production risk - especially for foreseeable misuse where improper use of a product could be reasonably foreseen.

Combining processes

Combining the requirements of ISO 12100:2010 and ISO 14971:2019 enables an RUO product to benefit from presumption of conformity against the machinery directive (2006/42/EC) and the IVD product to satisfy EU IVDR (2017/746).

In early stages of development, where the risk management activities focus upon electrical and mechanical safety, the requirements of ISO 12100:2010 are foremost. This ensures that the foundation of products destined for both RUO and IVD products are safe to use.

In later stages of the risk assessment, ISO 14971:2019 can be applied. Whilst not strictly necessary for a RUO product, the similarity of environment in which the products are used means the risk assessment inevitably benefits from the increased rigour of ISO 14971:2019.

For platform based IVD products where diagnosis is determined by the assay type, a separate risk analysis is required for each platform/assay combination. In this case, where the platform consists of instruments and consumables, risk management for an IVD product takes the RUO risk assessment as a starting point, but is then heavily influenced by regulation around the sample type and disease being diagnosed.

Processes at SMi

SMi's RUO platform shares identical hardware and materially similar software with that of its diagnostic platform, although user-defined parameters are disabled to ensure experimental consistency. This enables the RUO platform to be used for biomedical research and for research leading to the development of diagnostics (**Fig 2**).

The integration of design and manufacturing processes therefore gives users the confidence that RUO instruments and consumables conform to IVD regulatory standards and can be later used for IVD certification.

For both platforms the alignment of the risk processes also ensures that relevant controls can be implemented on both systems:

(1) instrument controls ensure that hardware is functioning within defined boundaries

(2) user controls assert the validity of user-dependent steps that could invalidate results when not performed correctly

(3) sample controls confirm sample integrity, such as the use of human DNA in COVID-19 PCR tests to confirm that a patient sample was taken

From a risk management perspective, designing these controls in at the system level provides risk mitigation which can be relied upon during later steps of diagnostic use. Even where a diagnostic is not the final goal, it offers integrated quality control features that provide assurance that the highest experimental standards are being met.

SMi sees operational advantages of combining the requirements and documentation of risk management standards in one risk management process. These advantages also enable a pipeline to support research innovation for the development of future diagnostic tests by the broader research community and can significantly reduce the technology barriers in diagnostic development.

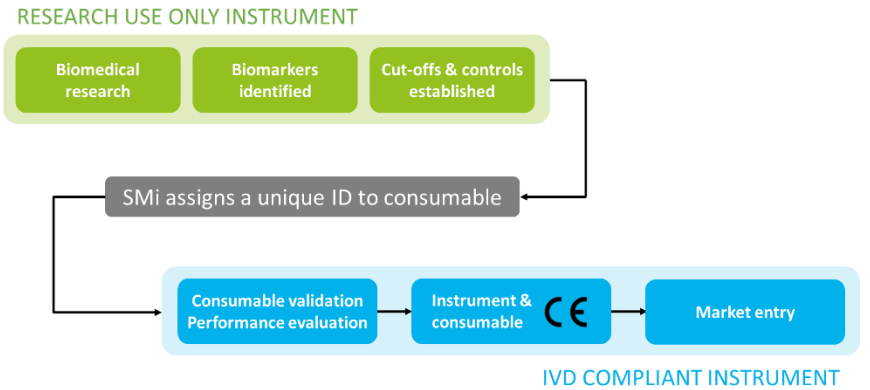

Fig 2 | SMi's pipeline enables assay development to be conducted on RUO products before transfer to a regulated IVD platform.