MANUFACTURER A-SERIES
SAFETY COLLECTION

12 information sheets answering
12 safety relevant questions on
the new Regulation on
Medical Devices (MDR)

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BASIC 24

What does a manufacturer need to do to place a safe and well performing medical device on the market?

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The MDR prescribes manifold obligations for manufacturers. Most of them are formal and are dealt with in the separate information sheet *"BASIC 16 - What are the formal steps a manufacturer needs to take to place a medical device on the EU market under the MDR?"*. Many substantive obligations are dealt with in other sheets, e.g. on General Safety and Performance Requirements. This sheet provides something different: a high-level structure for the management of a medical device. The principles in this section can support the improvement of the safety and performance of a medical device.

1. COLLECT INFORMATION relevant for safety and performance of medical device types that you deal with

There are different types of information relevant to safety: scientific, technological, or legal. Useful information can stem from authorities' alerts, even if these concern your competitors' products and not yours. Useful information can also be provided by medical professional societies or health insurances.
You should also collect information regarding alternative treatments. Even if your medical device is the best on the market, it might be regarded as unsafe or underperforming in the light of alternative treatments not involving the use of medical device of your type. (This type of information ihas only very limited relevance under the MDR. However, it is very relevant in terms of reimbursement and reputation.)

2. SELECT PARTNERS who are trustworthy and strong and who have high safety and compliance standards

Your devices' performance in terms of safety and performance does not only depend on your competence, your engagement and attitudes, but also on the competence, the engagement and the attitudes of your partners. These partners may be e.g.:

- specialised media;
- regulatory advisors;
- sponsors (of clinical investigations);

- persons responsible for regulatory compliance;
- Notified Bodies;
- Authorised Representatives;
- test houses;
- engineering service providers;
- production service providers;
- sterilisers;
- storage service providers;
- packagers;
- carriers;
- importers;
- distributors.

3. REDUCE ANY RISKS, and thus also the ones not explicitly mentioned in the MDR

The specific risk-related requirements of the MDR and the standards deal only with certain defined risks. This is dangerous. With ever more technological and human use aspects, unexpected new risks might arise. Partners may be the source of risks as well. Risks may also be very atypical and be outside the awareness of engineers, such as the risk of psychological dependence. In particular, you should strive to prevent unintended use of your device Many of the worst risks relate to use forms which are not intended by the manufacturer. By creative design or distribution conditions manufacturers can sometimes prevent unintended use.

4. Keep in mind the benefit-risk OPTIMISATION as the overall goal of the MDR

Even a high risk can be acceptable if the overall survival rate for a certain medical indication is increased by an innovative medical device. The obligation to reduce risks as much as possible has an important exception, see the new Section 2. of Annex I to the MDR which states:

> *"The requirements in this Annex to reduce risks as far as possible means the reduction of risks as far as possible without adversely affecting the benefit-risk ratio."*

For more details, see our sheet *"ESSENCE 40 - What does it mean "to reduce [a certain risk] as much as possible"?"*.

5. COMMUNICATE ON ISSUES

Sweeping problems under the carpet has rarely solved them. By addressing safety and performance related issues openly, you create a culture of risk reduction within your company and in relation to your partners which at the end of the day will improve safety and performance of all your devices. If you do the same towards your customers, you will build additional trust. Furthermore, you will also receive information that will help you to further improve your products.

6. REVIEW periodically and when there are reasons to do so

Review a number of areas periodically. Not all areas which will merit periodic revision in your case are listed here. But among those particularly recommended to be reviewed are the following: your compliance strategy, your risk management, your quality management, the scientific and engineering literature, the safety warnings of authorities, the list of your partners, the individual risk assessments, possibilities for benefit-risk optimisation, your communication practice and, last but not least, your respect of the principles listed in this sheet!

ESSENCE 8

Which are the most important rules when applying the General Safety and Performance Requirements?

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The "General Safety and Performance Requirements" (GSPR) are the device requirements listed in Annex I to the MDR. They replace the so-called "Essential Requirements" contained in the first Annex of each Directive.

- Link your examination as much as possible to your clinical documentation.
- Link your examination to scientific or engineering literature.
- Compare your risk control measures to those of competitors to be sure that you have reduced risks as much as possible.
- Interpret the specific GSPR in Chapters II and III of Annex I in the light of the general ones in Chapter I.
- Examine the GSPR of Chapter II before examining those of Chapter III. Reason: Information on risks cannot be appropriately formulated without having examined these risks.
- Examine the Machinery Directive requirements (applicable according to Article 1(12) MDR) and the GSPR of Chapters II and III before examining those of Chapter I. Reason: some of the GSPR of Chapter I can only be fulfilled after having fulfilled GSPR of Chapters II and III and the requirements of the Machinery Directive 2006/42/EC.
- Examine the GSPR of Section 23 in the light of its first Subsection 23.1.
- Keep the priority of Subsection 23.1(b) in mind: if possible and practicable, information is to be placed on the device. Manufacturers have more leeway only if this is not the case.
- Be careful when applying standards: standards touching on labelling and instructions for use do not necessarily reflect the priority order intended by the legislator. Some other standards give the manufacturers discretionary power not intended by the legislator.
- To interpret the word "appropriate" in Subsection 23.1(b) paragraph and elsewhere, ask yourself: "Where does the information need to be placed to best inform the user / patient?"
- If possible, and especially in case of doubt , place the information on the device and on the packaging of each device and on the packaging for multiple devices to avoid any discussions with Notified Bodies and authorities.
- If you expect that your medical device is likely to fail with regard to a particular GSPR, it might be more efficient to examine first the fulfilment of this very GSPR.
- Examine the GSPR in the light of the two most important risk management principles of the MDR: overall risk reduction + benefit-risk optimisation.

ESSENCE 16

Which main risk management obligations are contained in the General Safety and Performance Requirements?

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A. The general obligation to undertake risk management based on a risk management system

The most important obligation of manufacturers is the newly introduced duty to "*establish, implement, document and maintain a risk management system*", see Section 3 of Annex I to the MDR. No such obligation was contained in the MDD. Manufacturers thus need to create an organisational system which ensures that risk management is properly undertaken. The system needs to be updated from time to time (see "requiring regular systematic update" in the following definition).

B. Particular obligations regarding risk management

Risk management is defined as

> *"a continuous iterative process throughout the entire lifecycle of a device, requiring regular systematic updating. In carrying out risk management manufacturers shall:*
> *(a) establish and document a risk management plan for each device;*
> *(b) identify and analyse the known and foreseeable hazards associated with each device;*
> *(c) estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse;*
> *(d) eliminate or control the risks referred to in point (c) in accordance with the requirements of Section 4;*
> *(e) evaluate the impact of information from the production phase and, in particular, from the post-market surveillance system on hazards and the frequency of occurrence thereof, on estimates of their associated risks, as well as on the overall risk, benefit-risk ratio and risk acceptability; and*
> *(f) based on the evaluation of the impact of the information referred to in point (e), if necessary amend control measures in line with the requirements of Section 4."*

A number of conclusions and individual obligations can be drawn from this definition:

1. Risk management goes beyond the production. It needs to be continued even after the last (specimen of the) device has been placed on the market ("entire lifecycle of a device"). The obligation to undertake risk management ends only when the last (specimen of the) device placed

on the market or put into service is unlikely to be in use any more.

2. Risk management needs to be a continuous process for each device (type).

3. As the first step, risk management starts with the identification and analysis of “known and foreseeable hazards”.

4. All foreseeable hazards need to be taken into account in this first step, not just the ones known from the beginning. Hence it is necessary to actively look for hazards.

5. As the second step, manufacturers need to estimate the risks associated with each hazard. Risk is defined as “the combination of the probability of occurrence of harm and the severity of that harm” (Point (23) of Article 2). The word “combination” is to be understood as “multiplication” if the manufacturer has attributed quantitative values to the severity of harms. In this case, the overall risk assessment for a particular device can be expressed as:

severity of harm of hazard A x likelihood of hazard A occurring
+
severity of harm of hazard B x likelihood of hazard B occurring
+
severity of harm of hazard C x likelihood of hazard C occurring
+
…
= overall risk.

6. When estimating risks, manufacturers need to include risks which arise during reasonably foreseeable misuse and unintended use (but see our different statement for the benefit-risk determination).

7. As the third step, manufacturers need to eliminate or, if this is not possible, reduce (“control”) these risks, and thereby again also the risks which arise from reasonably foreseeable misuse or unintended use. By creative design or distribution conditions, i.e. ensuring that the devices only end up in the right hands, manufacturers can sometimes prevent misuse or unintended use.

8. Once production has started, risk-relevant information from production must be evaluated (first two steps) and reflected in the risk elimination or control measures (step 3). In substance, this is not an additional step, but simply the reiteration of the first three steps.

9. The same applies to risk-relevant information from the post-market surveillance system. Risk-relevant information must be evaluated (first two steps) and reflected in the risk elimination or control measures (step 3).

The risk management obligations of the MDR are process requirements. These process requirements are to be distinguished from the result requirements such as “risks reduced as much as possible” or “positive benefit-risk ratio/balance”.

Points 1 to 9 contain the essence of what the legislator instructs manufacturers to do. If you understand these points, you should be able to develop your own risk management system, even without using EN ISO 14971 or other standards. For a more detailed analysis, see our separate question *”ESSENCE 32 - Is it useful to apply EN ISO 14971 on risk management?”.*

C. Subset: risk control obligations

Unfortunately, the risk control obligations, a subset of the third step, are not easy to understand. The obligations contained in Sections 4. and 5 of Annex I to the MDR contain a mixture of process requirements (hereafter: “P”) and result requirements (hereafter: “R”). To facilitate understanding, one can consider the different elements contained in these sections separately and reformulate them into questions:

1. R: Do risk control measures adopted by the manufacturer for the design and construction of the devices conform to safety principles?

2. R: Have the safety principles been interpreted in accordance with the generally acknowledged state of the art?

3. P: Has the manufacturer undertaken an exercise to reduce all the risks associated with each hazard?

4. P: Has the manufacturer made a statement according to which he judges each individual residual risk as acceptable?

5. R: Is each individual residual risk acceptable?

6. P: Has the manufacturer made a statement according to which he judges the overall individual residual risk as acceptable?

7. R: Is the overall residual risk acceptable?

8. P: When planning and executing his risk reduction exercise, has the manufacturer respected the following priority order:
   - eliminate or reduce risks as far as possible and appropriate through safe design and construction;
   - where appropriate, take adequate protection measures, including alarms if necessary, in relation to risks that cannot be eliminated; and
   - provide information for safety (warnings/precautions/contraindications) and, where appropriate, training to users?

9. R: Have risks been eliminated or at least reduced as much as possible through safe design and construction? (Please note that risks should not be reduced to an extent that affects negatively the benefit-risk ratio – Section 2 of Annex I)

10. R: Have risks been reduced as much as possible by taking adequate protection measures, including alarms if necessary?

11. R: Has information for safety (warnings/precautions/contraindications) been provided?

12. P/R: Is training appropriate? And if so, has it been provided?

13. P/R: Has the manufacturer informed users of any residual risks?

14. R: With regard to use errors: have risks related to the ergonomic features of the device and the

environment in which the device is intended to be used been reduced as far as possible (design for patient safety)?

15. P/R: When leading the exercise aiming at the result described in 14., has the manufacturer taken account of the technical knowledge, experience, education, training and use environment (where applicable) and the medical and physical conditions of intended users (design for lay, professional, disabled or other users)?

It goes without saying that several recommendations made for the examination of General Safety and Performance Requirements also apply in the context of risk management. Here are three of them:

- Link your examination to your clinical documentation as far as possible.
- Link your examination to scientific or engineering literature.
- Compare your risk control measures to those of competitors (to make sure you have not missed opportunities to further reduce risks).

ESSENCE 40

What does it mean “to reduce [a certain risk] as much as possible”?

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In a public consultation prior to the adoption of its proposal, the European Commission has raised the question of whether the future MDR should be based on the so-called ALARP principle (risk-reduction As Low As Reasonably Possible) or whether the core principle of the MDD should be maintained. Based on the feedback from stakeholders and from Member States, the European Commission maintained the core principle of the MDD[1]: risk reduction as much as possible. The legislator has agreed with this. However, the Council introduced an exception to the rule of maximal risk reduction in Section 2. of Annex I to the MDR which states:

> *“The requirements in this Annex to reduce risks as far as possible means the reduction of risks as far as possible without adversely affecting the benefit-risk ratio.”*

This provision aims at covering situations where maximal reduction of Risk A might have:

(a) a disproportionately negative effect with regard to a Risks B, C, D, …, or
(b) a disproportionately negative effect on the medical efficacy of the MD, or
(c) some negative effect with regard to Risks B, C, D, … and some negative effect on the medical efficacy so that there is an overall negative effect of maximal reduction of Risk A.

1 See the impact assessment published together with the proposal.

Besides this exception, manufacturers thus need to apply the principle of maximal risk reduction. But what does this mean in practice? Will manufacturers be requested to do ever more in terms of safety so that medical devices will become too expensive? Such was the fear expressed by industry lobbyists before and during the adoption procedure. To find an answer to these questions, let's analyse how authorities are likely to decide:

> *Example A:*
> *All the devices on the market reach the same level of risk reduction. Further risk reduction would in theory be possible, but would massively increase the costs. In such a situation, authorities are extremely unlikely to request further risk reduction, even if they came to know that further risk reduction is possible.*
>
> *Example B:*
> *All the devices on the market reach the same level of risk reduction. Further risk reduction would easily be possible and would not be very expensive. In such a situation, authorities are likely to request further risk reduction, if they come to know that further cheap risk reduction is possible.*
>
> *Example C:*
> *Most devices on the market reach the same level of risk reduction, but some are better in terms of risk reduction. This makes them more expensive. In such a situation, authorities are likely to request further risk reduction from the majority of manufacturers so as to reach the level of risk reduction of the front-runners. The price is not an argument. Price increases due to new safety requirements are quickly compensated by economies of scale.*

In essence, the authorities are unlikely to request ever more radical risk reduction at exorbitant costs. But authorities might request that manufacturers to:

- not fall behind the risk reduction level reached by competitors;
- use the opportunity to reduce risks further if the further risk reduction is attainable and not too expensive, even if no competitor has so far used this opportunity.

Why has the legislator not accepted the ALARP principle which can be understood in quite the same way? Supposedly the legislator has done so to ensure a better position for authorities at the level of enforcement. To place the ALARP principle into the law would have substantially weakened the authorities at the level of enforcement. It would have exposed them to the risk of endless discussions and legal fights on what is “reasonably possible”. But in essence the minds of the two sides (authorities and industry) might not be as far away from each other as it seems at first sight.

ESSENCE 48

Under which conditions may less than maximal risk reduction be legitimate?

The answer to this question has been built into the information sheet *“ESSENCE 40 - What does it mean “to reduce [a certain risk] as much as possible”?”.*

ESSENCE 56

How to establish the benefit-risk balance?

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The final step of the risk management exercise and also of the application of all the General Safety and Performance Requirements is the overall benefit risk balancing.

A. The risk side of the balance

In the information sheet on major risk management obligations, it is stated:

> *5. As the second step, manufacturers need to estimate the risks associated with each hazard. Risk is defined as "the combination of the probability of occurrence of harm and the severity of that harm" (Point (23) of Article 2). The word "combination" is to be understood as "multiplication" if the manufacturer has attributed quantitative values to the severity of harms. In this case, the overall risk for a particular device can be expressed as: severity of harm of hazard A x likelihood of hazard A occurring + severity of harm of hazard B x likelihood of hazard B occurring + severity of harm of hazard C x likelihood of hazard C occurring + … = overall risk.*

This short text describes what is to be placed on the left side of the balance. All risks combined shall be placed on the left side of the balance. Are all risks really to be considered? There is an exception. Whereas the risk identification and control obligations also refer to risks linked to use which was not intended by the manufacturer, the overall benefit-risk determination must only include the risks linked to the intended use. The reason for this is a matter of fairness. It is not fair to prevent a manufacturer from placing a product on the market just because some people might use it for the delivery of illicit drugs. It would also be unfair to withhold a medical benefit from the patient just because the device could be used in a way other than intended by the manufacturer. Fortunately, the definition of 'benefit-risk determination' contained in Point (24) of Article 2 and the wording of Section 8 of Annex I to the MDR endorse this interpretation. Section 8 of Annex I to the MDR states:

> *"All known and foreseeable risks, and any undesirable side-effects, shall be minimised and be acceptable where weighed against the evaluated benefits to the patient and/or user arising from the achieved performance of the device during normal conditions of use."*

The words "during normal conditions of use" imply that the general use intention of the manufacturer is respected. However, "normal conditions of use" include user mistakes (unintended misuse). In particular, if the manufacturer issues over-complicated use instructions that users

easily misunderstand, he/she cannot argue that risks derived from use mistakes are not to be included in benefit-risk balancing. Some manufacturers have drawn appropriate conclusions from this. They sell their devices only to surgeons who have undergone proper training. Thus they reduce the risks "during normal conditions of use" so that the benefit-risk balancing is more in their favour.

B. The right side of the balance: the medical benefit

The medical benefit is an abstract term. A few cases may explain better the philosophy of the benefit-risk balancing.

> *Case 1: An implantable medical device always performs the function intended by the manufacturer (widening of a blood vessel) but succeeds to reduce the risk of fatal stroke by 80% in 525 % of the cases. In all other cases, there is no positive effect. Thus the medical benefit (fatal stroke avoidance) is reached in only 20% of all cases. What to put on the right side of the balance? The value of 1 life divided by 5.*
>
> *Case 2: A wound-care material produces the medical benefit of "substantial pain relief" in 60% of all cases. What to put on the right side of the balance? The value of "substantial pain relief" x 0.6 (or 60%).*
>
> *Case 3: A wound-care material produces the first medical benefit of "substantial pain relief" in 60% of all cases and the second medical benefit of "reduction of the risk of infection from 40% to 10%" in 50% of all cases. What to put on the right side of the balance? For the first medical benefit, the value of "substantial pain relief" x 0.6 (or 60%). Plus, for the second medical benefit: 30% infection risk reduction in every second case = 15% overall infection risk reduction.*

This brings us to the overall conclusion on what to put on the right side of the balance. It is something very similar to what we have seen for the risk side of the balance. The medical benefit can be defined as "the combination of the probability of occurrence of a positive medical effect and the value of that positive medical effect". Again the word "combination" is to be understood as "multiplication" if the manufacturer has attributed quantitative values to the extent of the benefit. In this case, the overall medical benefit for a particular device can be expressed as follows:

(value of) medical benefit A x likelihood of medical benefit A occurring
+
(value of) medical benefit B x likelihood of medical benefit B occurring
+
(value of) medical benefit C x likelihood of medical benefit C occurring
+
…
= overall medical benefit

C. Quantitative values help

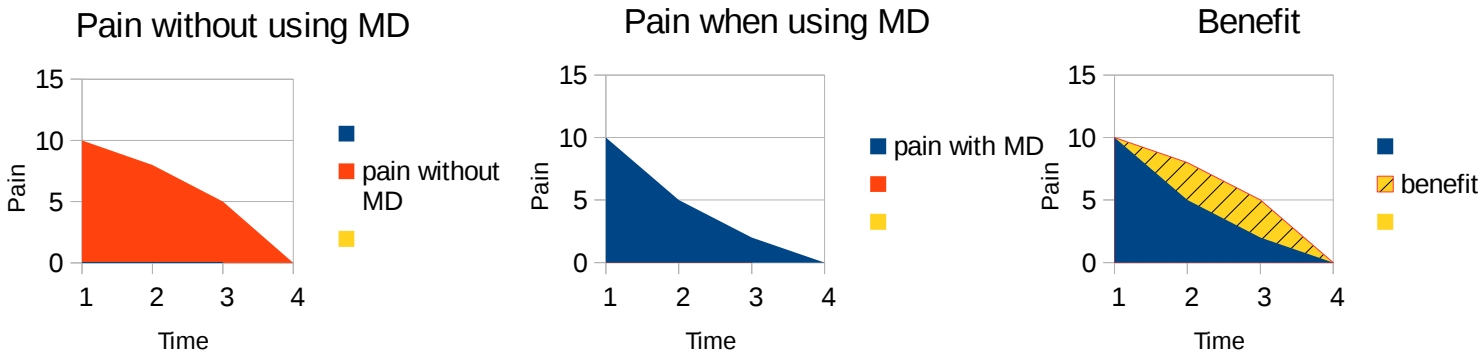
It might seem difficult or even arbitrary to attribute quantitative values to hazards and medical benefits. However, forcing oneself to attribute quantitative values leads to a more rigorous thinking. If it was common practice to use quantitative values, there could be a discussion amongst stakeholders and authorities, if not the entire society, on how to value hazards and medical benefits. What is the quantitative value to be attributed to 100 days with full pain (rated 10 out of 10

by the patients)? Does these 100 painful days already reach the same negative value as death? We guess rather not. Or is the negative value of death reached after 10.000 days of full pain? We could imagine that it is, but a shorter time period should be the reference if life expectancy is lower.

If you were to follow more or less the (of course debatable) statements made in these few lines, you would need to draw the following conclusions:

- Minor improvements of medical conditions, even where lasting for the rest of the life, can hardly justify even a 1/10.000 death risk.
- Minor improvements of medical conditions, even where lasting for the rest of the life, can hardly justify even a 1/10.000 risk of full pain for the rest of a person's life.
- Minor improvements of medical conditions such as minor pain relief, if lasting only for a day, can hardly justify a 1/10.000 risk of medium life-long pain.

This brings us to the importance of the factor of time. If we scale negative deviation from normal well-being from 1 to 10 (with 10 representing the full pain) on the y-axis, we can also scale the time on the the x-axis. This allows us to understand medical benefit in case of pain-relief as the difference between the integral of the curve representing the pain relief without intervention of the medical device:



Estimating the negative deviation from the normal state of well-being over time and expressing it graphically might thus become key for understandable communication on medical benefit.

D. No comparison with other devices or treatments

There is no need any more to discuss whether benefit-risk balancing is influenced by alternative medical treatments. Proposals to insert such an element into the MDR were not followed: there is no element in the text of the MDR that would favour an interpretation according to which benefit-risk balancing needs to reflect alternative treatments[2]. Thus the question of comparative utility of the medical device versus other medical devices or alternative treatments is left to the sphere of health technology assessment and reimbursement. Some findings on the General Safety and Performance Requirements and the clinical evaluation (which must include some comparative elements) create a bridge towards the world of health-technology assessment and reimbursement. But neither the manufacturer nor the Notified Bodies are asked to compare utility and risks in the framework of the benefit-risk balancing. Rightly so because at best the reimbursing institutions dispose of the data needed for such a comparative analysis.

2 Except maybe Article 61(3)(c), the meaning of which is explained in the information sheet "CLINIC 112".

ESSENCE 64

Are risks linked to unintended use to be taken into account when establishing the benefit-risk balance?

The answer to this question has been built into the information sheet *"ESSENCE 56 – How to establish the benefit-risk balance?".*

ESSENCE 72

If a supplier or his Notified Body has tested crucial components of a device against some General Safety and Performance Requirements, does the manufacturer need to repeat the tests and make his own assessment against the General Safety and Performance Requirements?

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There are various reasons why it is not necessarily sufficient for a manufacturer to refer to the assessment of General Safety and Performance Requirements (see Annex I to the MDR) undertaken by the supplier of a crucial component (or his Notified Body):

1. Most General Safety and Performance Requirements (GSPR) oblige the manufacturer to reduce risks as much as possible. This obligation is incumbent on the manufacturer, not on his supplier. Even if the supplier has taken the applicable General Safety and Performance Requirements into account when designing his component, the supplier has not done so for the entire device. E.g., it might be that more General Safety and Performance Requirements apply to the entire device (also with regard to the component) than to the component alone. It can even be that a component with maximal risk reduction under average conditions has higher risks than another component where built in a device with certain particular features.

2. Even if the component has been optimised, other components based on a different design and manufactured by another supplier might be perform better in terms of risk reduction or benefit-risk optimisation. They can be better in general or in view of the precise device in question.

3. There might be design alternatives to the use of the component type in question. The

examination of even the best possible component of the type in question does thus not necessarily lead to the fulfilment of the GSPR by the device as such.

4. The quality system requirements may create a legal obstacle. At least for conformity assessment in accordance with Annex IX, it is necessary to integrate the supplier of crucial components into the Quality Management System of the manufacturer. Otherwise the obligation to maintain a comprehensive Quality Management System can be circumvented by outsourcing. The situation is less clear in case of conformity assessment in accordance with Annexes X and XI where there is no provision similar to the third indent of Section 2.2.(b) of Annex IX, which reads:

> *"...where the design, manufacture and/or final verification and testing of the devices, or parts of any of those processes, is carried out by another party, the methods of monitoring the efficient operation of the quality management system and in particular the type and extent of control applied to the other party, and ...".*

But all this does not preclude that the result of an individual test, undertaken

- by a certified test house on behalf of the supplier, or
- by the supplier's Notified Body, or
- by the supplier himself under surveillance of either the test house or the supplier's Notified Body

can be taken into account when the manufacturer assesses his device against the General Safety and Performance Requirements. Of course, the test undertaken can be a valuable source of information, if it was done / performed in a methodologically correct way.

Furthermore, if
(a) there are no Quality Management System reasons prohibiting this, and
(b) the test was methodologically correct, and
(c) the conditions of the test were such that cheating is extremely unlikely, and
(d) the test of component is equally conclusive for the final device as it was for the component,
there is nothing in the MDR obliging the manufacturer of the medical device to repeat the test previously undertaken. The last condition is met in particular where the test was undertaken or observed by a certified test house or a Notified Body.

It goes without saying that the manufacturer is still responsible for the fulfilment of legal requirements even where a crucial component was tested in accordance with these rules. Nothing protects his "good faith". Therefore, the manufacturer should critically review the test.

To sum up:

- The manufacturer must perform his own assessment of the fulfilment of the General Safety and Performance Requirements. He cannot refer to the supplier's assessment.
- Under certain conditions, the manufacturer may use the results of the test undertaken by his supplier.
- Under further conditions he may even refrain from performing his own tests.

ESSENCE 88

What level of performance does a medical device need to reach?

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There are two provisions in the MDR which refer to the performance of medical devices in particular:

A. Section 1 of Annex I to the MDR stipulates:

> *"Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose. They shall be safe and effective and ..."*

Various conclusions can be drawn from this provision:

1. The manufacturer himself determines the performance the device must achieve. If he intends a low level of performance, his device must only reach this low level of performance. If he intends a high level of performance, his devices must reach this high level of performance. When determining the intention of the manufacturer, Notified Bodies or authorities may take the technical documentation, the instructions for use and promotional material into account (general rule and practice under the MDD already). In addition, the clinical evaluation determines the intended purpose under the MDR, see the definition of intended purpose.

2. As a rule, there is no obligation to reach a high level of performance or just even a "state-of-the-art" level of performance, unless Common Specifications oblige the manufacturer to do so. It was decided to drop the performance-related "state-of-the-art" requirement in the course of the legislative procedure.

3. However, there is a minimum benchmark. As indicated by the parts *"... and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose."*, the device must serve the intended purpose effectively. This is confirmed by the criterion "effective" in the next sentence. This means: If the intended purpose is pain reduction, the device must reduce the pain at least to some extent. It may, however, be comparatively inefficient in doing so. See also the newly introduced Article 7 which confirms this result.

4. This interpretative result might seem astonishing at first sight. However, it is not new at all. Already under the MDD, there was no performance-related "state-of-the-art"-requirement for medical devices. Only for *in vitro* diagnostic medical devices, for which there were Common

Technical Specifications, there could have been such a performance requirement. The logic behind this conscious decision is that the legislator sets up a high benchmark in terms of safety. But an equally high benchmark for performance would eliminate too many products from the market, to the detriment of less rich patients and less rich national economies.

5. However, the legislator has indirectly established a minimum performance threshold. The 2nd sentence of Section 1 of Annex I to the MDR sets up a state-of-the-art-requirement for the benefit -risk ratio:

> *"They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks where weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art."*

This implies indirectly that the performance may not be too low: otherwise the ratio would be too bad to make the medical device pass the threshold of the state of the art for the benefit-risk ratio.

B. Furthermore, Section 6 of Annex I to the MDR contains a requirement regarding the maintenance of the performance:

> *"The characteristics and performances of a device shall not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, where the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions."*

Whereas the Section 1, analysed under "A.", deals with the initial performance of the medical device, this Section 6 relates to the continuity of this performance under normal conditions of use during the lifetime of the device.

Again, the manufacturer has quite some discretionary power. He may indicate the lifetime of the device and the maintenance requirements. But he may not issue unrealistic or completely surprising indications without abusing this discretionary power. Furthermore, manufacturers must be consistent in their indications, including those they make in their promotional material.

ESSENCE 96

What does the "state-of-the-art" requirement refer to? (partly overlapping with ESSENCE 88)

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- *the legal views taken in this text will be followed by all courts;*
- *the recommendations given in this text will necessarily lead to the best possible outcome.*

Accordingly, readers cannot hold the authors liable.

A. Not applicable to performance

The "state-of-the-art" requirement does not refer to the performance of the devices. The initial proposal of the European Commission contained the following requirement:

> *"Devices shall achieve the performance intended by the manufacturer and be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose, taking into account the generally acknowledged state of the art. They shall be safe and effective and ..."*

The final Section 1 of Annex I to the MDR, however, just reads as follows:

> *"Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose. They shall be safe and effective and ..."*

Thus it was decided to drop the "state-of-the-art" requirement. This interpretative result might seem astonishing at first sight. However, it is not new at all. Already under the MDD, there was no "state-of-the-art" requirement for medical devices. Only for *in vitro* diagnostic medical devices, for which there were Common Technical Specifications, there could have been such a performance requirement. The logic behind this decision is that in terms of safety, the legislator sets up a high benchmark. But an equally high benchmark for performance would eliminate too many products from the market, to the detriment of less rich patients and national economies.

However, as we will see under "B.", there is a state-of-the-art requirement for the benefit-risk ratio. This implies indirectly that the performance may not be too low: otherwise the ratio would be too bad to pass the threshold of the state of the art.

B. State-of-the-art requirement for the benefit-risk ratio

The 2nd sentence of Section 1 of Annex I to the MDR sets up a state-of-the-art requirement for the benefit-risk ratio:

> *"They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks where weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art."*

C. State-of-the-art requirement for risk reduction

Section 4 of Annex I to the MDR obliges manufacturers to take into account the state of the art where adopting risk control measures:

> *"risk control measures adopted by manufacturers for the design and construction of the devices shall conform to safety principles, taking account of the generally acknowledged state of the art."*

D. State-of-the-art requirement for software

Section 17.2 of Annex I to the MDR contains a specific state-of-the-art requirement for software:

> *"17.2. For devices that incorporate software or for software that are devices in themselves, the software shall be developed and manufactured in accordance with the state of the art taking into account the principles of development life cycle, risk management, including information security, verification and validation."*

E. State-of-the-art requirement for investigational devices

Article 62(4)l) on investigational devices contains a provision that refers to the state of the art as well:

> *l) "the investigational device(s) in question conform(s) to the applicable general safety and performance requirements set out in Annex I apart from the aspects covered by the clinical investigation and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the subjects. This includes, where appropriate, technical and biological safety testing and pre-clinical evaluation, as well as provisions in the field of occupational safety and accident prevention, taking into consideration the state of the art."*

Reading this provision to the letter, the state-of-the-art requirement is only applicable to the items listed in the last sentence. However, it can be expected that authorities apply the criterion on all aspects mentioned in Article 62(4)l).

ESSENCE 104

What does “state-of-the-art” mean?

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The term "state of the art" is used so often because it has two advantages:

- It aims at a high performance level;
- It is dynamic in time.

Unfortunately, there are uncertainties as to the use of this term: Does it mean that the highest possible level has to be fulfilled (interpretation A)? Or is it sufficient to fulfil a fairly high, not sub-standard level (interpretation B)?

Let us look at what the European Court of Justice (ECJ) has made of this expression. The ECJ has not given an interpretation of "state of the art". However, at the ECJ, various terms have been used in French which all have been translated by "state of the art". As French is an extremely important language in the court's day-to-day practice, it is worthwhile looking at these translations:

- C-6/05, ruling of 14 June 2007: *État de la technique généralement reconnue*: state of the generally recognised technology;
- C-183/95, ruling of 17 July 1997: *État actuel de la science*: current state of science;
- C-198/97, conclusions of the General Advocat of 16 Janvier 1999: *État optimal de la technologie*: optimal state of technology.

The last two quotations point towards the more stringent interpretation A, whereas the first is still open to interpretation B. To be on the safe side, manufacturers should thus strive for the “highest possible level”.

However, it is not certain that the medical devices authorities will follow this strict interpretation. E.g., the medical devices authorities were more lenient and followed interpretation B when deliberating on so far the only official case in which the state-of-the-art requirement was at stake. In 2008, the European Commission and the Member States analysed a Portuguese safeguard clause case regarding an Italian HIV test. To have a basis for their decisions, the authorities analysed the performance of more than 15 HIV tests. Corresponding to their age or “generation”, the tests grouped well into three bundles. Tests of the first generation were regarded as underperforming. Tests of the second generation were (at the time) still regarded as acceptable and the best second generation tests were almost as performing as the worst third generation tests. In 2008, the cut-off was made between the first and the second generation of the tests on the market at that given time. It was expected that the cut-off was to shift to between the second and

the third generation some years thereafter. For details, see this Decision of the European Commission.

To sum up: manufacturers can only be sure they are on the safe side if they follow the stricter of the two interpretations, but they may expect a less severe practice from the side of authorities.

CONCRET 64

What to care about once you have decided to use harmonised and listed standards to demonstrate compliance with legal requirements? (MDD+MDR)

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Once you have decided to use harmonised standards, the real work just starts. It might include the following steps, although this list does not claim to be comprehensive:

1. Check whether the standard you are about to acquire is under attack, e.g. by a Formal Objection. If so, your investment might not be worth it.

2. Check whether the standard you are about to acquire is in its final phase of revision. If so, consider waiting for the new version. A newer version of the standard might substantially redefine the state of the art. How to find out whether a new version is about to come? Work projects of the standardisation organisations are published on their websites (see here for CEN and for CENELEC). Some specialised media also report on them.

3. Check where you can buy the standard and at which cost! Subject to your language knowledge, you may acquire the EN (EU) standards from several national standardisation bodies which may have different prices.

4. Start with the legal requirements. Establish a list of the legal requirements you need to apply. Be aware of each individual aspect of a legal requirement (e.g. design, manufacturing and packing). You might use checklists like General Safety and Performance Requirements checklists elaborated by others, but be careful and double-check these tools.

5. Read the standards together with guidance elaborated by authorities, if any. Such guidance might partly correct the standard.

6. Check to what extent you can tick legal requirements off your list because you fulfilled the harmonised standard. For details on this, see the question *"CONCRET 48 - How to find out which presumption of conformity with legal requirements is provided by a standard?"*.

7. Read the respective legal requirements in parallel.
Interpret the standard "in the light of" the legal requirements. In case of contradictions, follow the legal requirements.

8. Perform gap analysis for the individual legal requirements:

- Are all the aspects of a certain legal requirement (e.g. dealing with design, manufacturing and packaging) covered?
- Does the standard include all necessary tests to claim the coverage of a certain legal requirement?
- Does the standard take sufficient account of atypical patient groups, technologies and device types? Is the standard complete and safe for all patients, technologies and device types?
- Does the standard still represent the state of the art? This is particularly problematic where a standard contains normative references to other old standards. But some old standards exceptionally do still represent the state of the art.

9. Correct the standard with regard to its deficient normative references:

E.g., if the standard contains normative references to outdated standards or standards which are not accessible any more, how can you reasonably replace the invalid normative references? Or, if the standard contains contradicting normative reference chains to different versions of the same standard, which normative reference chain is most appropriate to follow? Mostly, this will be the most recent version. However, sometimes the most recent version will be based on another technological approach that does not fit, in which case a less recent version needs to be applied.

10. Don't be lazy with regard to the normative references:

Several thousand pages of other standards are sometimes normatively referred to. This is the case in particular for EN IEC 60601-1 and those many standards which normatively refer to this standard. Normative reference chains in the EN IEC 60601 family are so complex that one can wonder how manufacturers find their way through it. However, to obtain the presumption of conformity, manufacturers need to follow the normative references.

11. Perform gap analysis for all the legal requirements:

Based on the gap analysis for each individual legal requirement, you may develop the overall gap analysis. This overall gap analysis is the bridge / interface to your compliance strategy, to be developed at least for all requirements not covered by the harmonised and listed standards applied.

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Kind regards,

The authors