Regulatory needs
Exchange of a PFAS containing manufacturing device (e.g. tube, filter …) with a PFAS free alternative

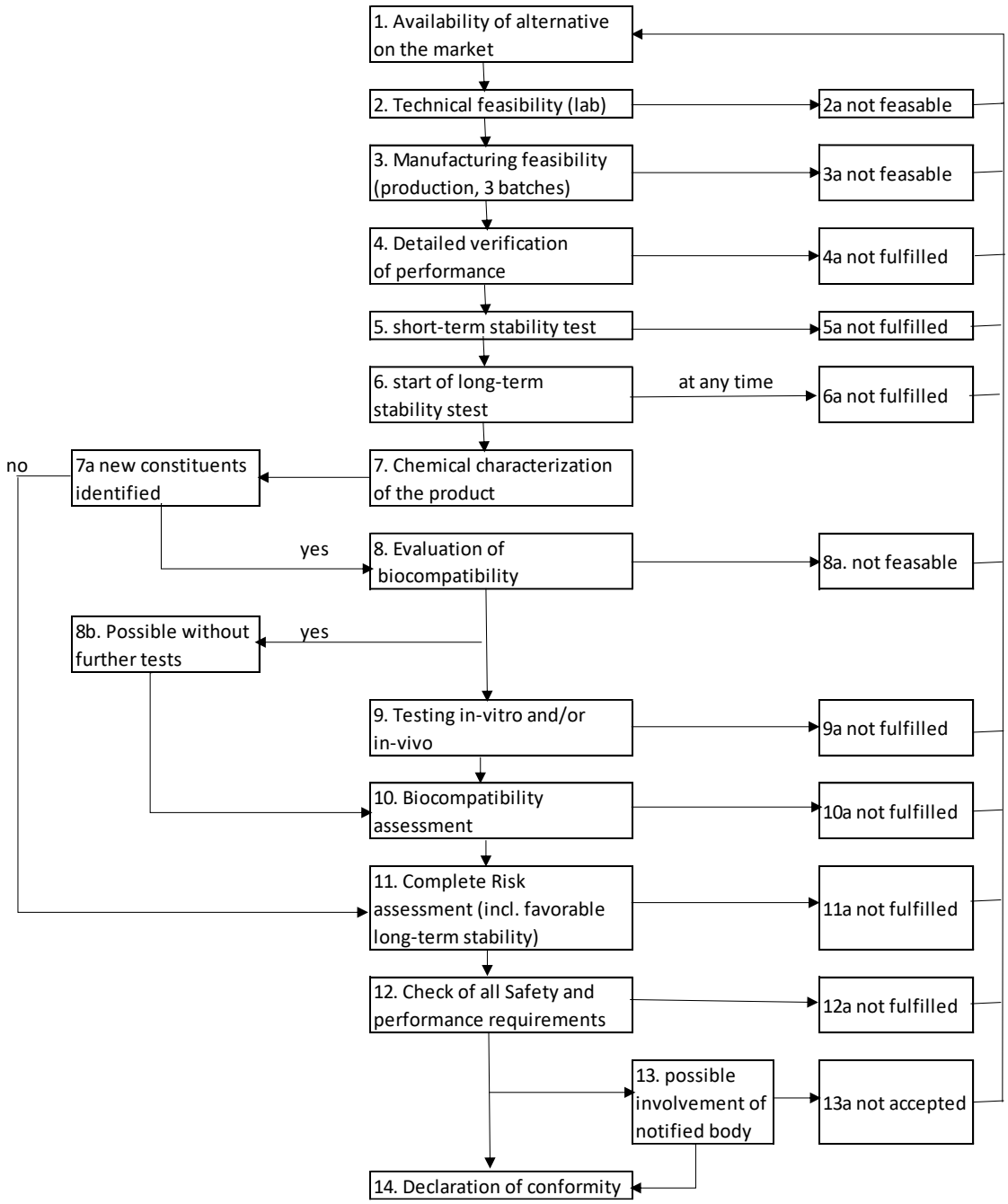
Introduction

Many medical devices may be affected by the restriction of PFAS in different ways. The following description shows different possibilities for being affected, without claiming to be complete.

- Some medical devices may contain PFAS as an intentionally added ingredient (e.g. some ophthalmic devices or devices containing PFAS-surfactants). The technical and regulatory challenges for a PFAS-replacement must be analyzed product by product (or product class) and are not in scope of this document.
- Many medical devices may contain PFAS-polymers or polymers with PFAS-coatings as constituent parts if the device (e.g. tubes for respiratory pathways, for blood, urine, nutrient, or pharmaceuticals transport, catheters, foils or containers used in 3D-printing etc.). Even if the technical issues for a replacement in such cases could be very challenging, the regulatory requirements are mostly the same as shown in this document.
- A more indirect affectedness is given for medical devices, for which PFAS-containing devices are used in the manufacturing process (e.g. tubes, filters, foils etc.). The regulatory requirements for the replacement of such parts are discussed in detail in this document.
- As well only indirectly affected are medical devices using substances either as constituents of the medical device or as production aids, that are manufactured by using either PFAS-containing aids (e.g. catalysts) or additives or PFAS-containing manufacturing devices. Even if in these cases the major technical challenges are on the side of the substance manufacturer, the regulatory challenges for the manufacturer of medical devices may be comparable to the requirements described below, if the impurity-profile of the substance is changed by the PFAS-replacement.

Even if there are no substantiated data available yet, it can be expected that a high number, if not even most, of the medical devices on the market are affected by at least one of the last three bullet points.

Flowchart



Discussion

Step	Discussion	Duration (month)		
		Min	Max	Comments
1	Could be 6.5y or 13.5 y after publication of the Restriction depending on the derogation			
2	First check of feasibility	1	4	Depending on the complexity of the replacement and possibly the number of affected products
2a	At practically any point it could be found that the alternative is not			

	feasible (the requirements are not fulfilled)			
3	Check of feasibility in the manufacturing environment. Usually 3 batches must be manufactured	2	9	Depending on complexity of the replacement, the availability of the manufacturing devices (e.g. use of the devices for other products as well) and possibly the number of affected products
4	Even if the basic performance was checked in step 2 a detailed performance check of products out of manufacturing process is required by MDR	(1)	(3)	Depending on the complexity of the replacement and possibly the number of affected products - included in the timing for step 5
5	Can be done in parallel with 4; however at least 3 months of stability are usually needed for a first evaluation	3	6	3 months after the start of the storage (in case of multiple products this timeline is defined by the last storage start)
6	Depends on the shelf-life of the product. Usually medical devices need a shelf-life of 18 – 48 months to be commercialized (favorable test results usually for 9 – 24 months at elevated temperatures). Long-term stability tests can be started in parallel to step 4 and 5	(9)	(24)	If the shelf life exceeds the timeline for all other further steps, they are determining the timeline
7	Requirement of ISO 10993-1 and 10993-18	1	6	Depending on the complexity of the product, the needs for preliminary tests, development of extraction and analytical methods, availability of lab capacity at specialized contract labs
7a	If no new constituents are identified in the product only the steps 11 – 13 are further relevant			
8	Based on the new constituents a first biocompatibility evaluation should be done to verify the need of testing an develop a test plan (ISO 10993-series)	1	3	Depending on the complexity of the replacement and possibly the number of affected products
8b	If no further tests are needed step 9 is obsolete			
9	Finalization of test plans, preparation of test specimens, clarification of test procedures with contract labs, testing and finalization of test reports by contract labs (ISO 10993-series; for respiratory pathways devices instead of ISO 10993-series the requirements of ISO 18562-series apply	3	18	Depending on the tests required based on the type of medical device, the concerns arising form new constituents (see ISO 10993-series), the number of products affected by the exchange, and the capacities of contract labs

10	Based on chemical characterization, data regarding tolerable intake of constituents and test results a biocompatibility assessment is prepared by a trained person (toxicologist)	1	2	In case of an external toxicologist, some discussion is needed in front, during and after development of the assessment
11	Risk assessment is done based on ISO 14971 by a group of product and safety experts	1	2	Depending on the complexity of the replacement and possibly the number of affected products
12	Final check of all safety and performance requirements of MDR Annex I by a group of regulatory and product specialists	1	2	Depending on the complexity of the replacement and possibly the number of affected products
13	In some cases (e.g. medical devices class III) the full technical documentation (manufacturing and quality documentation, documents mentioned above in the flowchart) must be verified first by the notified body (MDR)	2	6	Depending on the complexity of the replacement and possibly the number of affected products and the number of dossiers submitted in the same time to the notified body by different manufacturers
14	If no involvement of the notified body is needed, the Declaration of conformity can be prepared by the manufacturer after compilation of the technical documentation	1	2	Depending on the complexity of the replacement and possibly the number of affected products

Conclusion

For the case of replacement of a PFAS-containing manufacturing device with an PFAS-free alternative, no fix timeline can be established. A minimum and a maximum need of time for such a process from the regulatory perspective is given below.

If

- all steps lead directly to a favorable result
- there is only one or a very low number of medical devices affected by the replacement
- there are no multiple changes of manufacturing devices that would complicate the process
- no new constituents are identified by the chemical characterization
- no preliminary involvement of the notified body is needed

an absolute minimum of about 18 months is needed. If a longer shelf life as 18 months is required by customers, this minimum period will increase up to 33 months.

In case of

- many medical devices affected by the replacement
- identification of new constituents by the chemical characterization
- complex situation for chemical characterization
- need of long-term biological testing (e.g. subchronic toxicity (9 months *in vivo*) or implantation (min. 9 months *in vivo*)

the time period needed to fulfill the regulatory needs will increase to about 18 months till start of shelf-life testing plus 9 – 24 months of shelf-life tests. In parallel to these tests up to about 29 months are needed for the chemical characterization and biological tests. Additionally, about 6 months are needed for finalization of the steps 11, 12, and 14. This means that the total amount of time needed

for the regulatory requirements of such an exchange can increase up to about 53 months (more than 4 years).

In this calculation some aspects are not regarded:

- if a replacement fails due to unfavorable results at any time point, new replacements must be found. In a worst case this can more than double the time needed.
- if many manufacturers need at the same time chemical characterization and/ or biological testing the bottleneck could be the capacity of the contract labs, leading to delays of some months to 1 year or longer
- if many manufacturers need to involve the notified bodies at the same time for verification of such replacements in the technical documentation, the notified bodies may become as well a bottleneck (this fact already led to the extension of the time frame for implementation of MDR). Additional time up to some months or a year would be possible.
- in some cases, especially (but not limited to this) if a PFAS-constituent of the medical device is replaced, additionally to the regulatory steps shown in the flowchart above, a clinical trial could be necessary. In these cases additionally to the given timeline other ca. 2 – 5 years could be needed for the replacement.

Based on these considerations the derogation of 13.5 years for medical devices is very short, especially considering that the replacement would be available probably at the end of the derogation period for the manufacturing devices (probably 6.5 years, in some cases possibly 13.5 years). For this reason, for highly regulated products like medical devices a longer derogation is needed. We propose an additional derogation time of 5 - 10 years or at least an additional derogation time of 3 - 5 years for medical devices of class I, IIA and IIB and 5 - 10 years for medical devices of class III or devices with replacement of a PFAS-constituent. Even this will not cover fully the absolute worst cases that may occur. Only by such a longer derogation time the supply of vital medical devices to the health system can be guaranteed.