

COMMISSION DECISION (EU) 2018/1617**of 25 October 2018****concerning a measure adopted by France pursuant to Council Directive 93/42/EEC with regard to the Terrafor and Defiligne medical devices***(notified under document C(2018) 6943)***(Text with EEA relevance)**

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Council Directive 93/42/EEC of 14 June 1993 concerning medical devices ⁽¹⁾, and in particular Article 8(2) thereof,

Whereas:

1. PROCEDURE

- (1) On 16 August 2016, the French authorities adopted a decision based on the national provisions transposing Directive 93/42/EEC (hereinafter 'Directive 93/42/EEC' or 'the Directive') with regard to two medical devices with the same composition, the same route of administration and the same purposes, marketed under the names 'Terrafor' or 'Defiligne' (hereinafter 'the device'), and manufactured by the Claytone-Terrafor Laboratory (hereinafter 'the manufacturer').
- (2) The device in question takes the form of capsules administered orally, which, according to the instructions for use, 'prevent digestive problems, reduce digestive discomfort, restore digestive comfort and reduce abdominal circumference'. The substance used in manufacturing the device is Octalite, a mineral complex of natural origin (clay).
- (3) According to the decision taken by the French authorities, in view of the essential requirements of the Directive and given the presence of lead in the device, it may pose a risk to the health of users. As a consequence, the decision provides that 'the manufacture, placing on the market, distribution, export and use of the Terrafor and Defiligne medical devices [...] shall be suspended until the products have been brought into line with the legislative and regulatory provisions which apply to them'. Moreover, 'the Claytone-Terrafor laboratory is required to withdraw the Terrafor and Defiligne medical devices from all the distributors concerned'.
- (4) By letter of 4 October 2016, the French authorities notified the Commission of their decision of 16 August 2016 in the context of Directive 93/42/EEC.
- (5) As part of the consultations referred to in Article 8(2) of Directive 93/42/EEC, the Commission sent the manufacturer an email on 26 October 2016 asking it to state its position on the decision taken by the French authorities.
- (6) By letter of 30 November 2016, the manufacturer sent the Commission a memorandum setting out its reasons for contesting the decision taken by the French authorities.
- (7) On 19 December 2016, at the manufacturer's request, a meeting was held between the manufacturer and the Commission.
- (8) In the course of 2017, numerous e-mails were exchanged between the manufacturer and the Commission. In particular, the Commission asked the manufacturer several times to contact the French authorities in order to identify the information which would be necessary to allow the decision of those authorities to be lifted.
- (9) By email of 20 March 2017, the manufacturer sent the Commission a report from the NAMSA laboratory ⁽²⁾ which, according to the manufacturer, showed that the device was safe. The Commission asked the manufacturer several times to send that document to the French authorities. The manufacturer did so several months later, in August 2017. At the same time, the Commission exchanged e-mails with the French authorities in order to obtain further information.

⁽¹⁾ OJ L 169, 12.7.1993, p. 1.

⁽²⁾ This report is entitled 'Addendum to risk assessment No 164726 of 17 February 2017'.

- (10) In July 2017, the manufacturer submitted a complaint to the European Ombudsman concerning the Commission's delay in adopting a decision. On 5 April 2018, the Ombudsman decided to close the case, concluding that there had been no maladministration on the Commission's part in its handling of the case.
- (11) By email of 20 November 2017, the Belgian authorities notified the Commission of their decision of 28 October 2016 to prohibit the placing on the market, putting into service, distribution and importation of the Terrafor medical device, and to order the withdrawal of the device from the market.
- (12) On 7 February 2018, at the manufacturer's request, a meeting was held between the manufacturer, the French authorities, the Belgian authorities, the NAMSA laboratory and the Commission.
- (13) In March 2018, the Commission submitted additional written questions to the manufacturer, to its notified body (TÜV Rheinland LGA Products GmbH) and to the Belgian and French authorities. They replied to these questions during March and April 2018.

2. EXAMINATION OF THE JUSTIFICATION FOR THE MEASURE

- (14) Directive 93/42/EEC establishes a system under which medical devices must meet the essential requirements set out in Annex I to the Directive which apply to them (Article 3, first paragraph). In order to prove compliance with these essential requirements, the manufacturer must follow one of the conformity assessment procedures provided for in the Directive, which allows the CE marking to be affixed to the devices (Article 11 and Article 17(1)). Devices bearing the CE marking indicating that they have undergone a conformity assessment may move freely within the Union (Article 4(1)).
- (15) However, in accordance with Article 8 (safeguard clause) of Directive 93/42/EEC, 'where a Member State ascertains that the devices [...], when correctly installed, maintained and used for their intended purpose, may compromise the health and/or safety of patients, users or, where applicable, other persons, it shall take all appropriate interim measures to withdraw such devices from the market or prohibit or restrict their being placed on the market or put into service. The Member State shall immediately inform the Commission of any such measures, indicating the reasons for its decision [...]' (Article 8(1)). The Commission must then determine whether the measures are justified or not (Article 8(2)). It is therefore for the Member States to determine whether a product is liable to compromise the health and safety of persons and, if so, to take the requisite measures. Such an exercise may entail complex technical and scientific assessments on the part of the national authorities. It is for the Commission to verify whether or not these measures are justified, and in particular to make sure that the legal and factual reasons for their adoption are valid. The Commission enjoys wide discretion in this context ⁽¹⁾.
- (16) In the present case, in the decision and note notified on 4 October 2016, the French authorities take the view that the devices in question 'may pose a risk to health' and 'do not comply with the essential requirements'. However, where there is a risk to the health and/or safety of persons, resulting in particular from failure to comply with the essential requirements referred to in Annex I to Directive 93/42/EEC, a safeguard clause procedure may be initiated under Article 8(1) of that Directive ⁽²⁾. It follows that, in the present case, the safeguard clause procedure applies, with the result that it is for the Commission to determine whether the measure taken by the French authorities is justified or not.
- (17) The decision taken by the French authorities makes provision for suspension of the 'manufacture, placing on the market, distribution, exportation and use' of the device and its withdrawal from the distributors concerned. As Directive 93/42/EEC essentially provides that medical devices may be placed on the market and/or put into service only if they meet the requirements of the Directive (Article 2) and that the Member States must not create any obstacle to the placing on the market and/or the putting into service of devices which, in order to prove compliance with the requirements, have been the subject of an assessment of their conformity in accordance with the Directive (Article 4) and as Article 8 of the Directive requires the Member State concerned, where there is

⁽¹⁾ See in particular, regarding the safeguard clause of Directive 2006/42/EC of the European Parliament and of the Council of 17 May 2006 on machinery, and amending Directive 95/16/EC (OJ L 157, 9.6.2006, p. 24), the judgment of the General Court of 15 July 2015, *CSF v Commission*, T-337/13, ECLI:EU:T:2015:502, paragraphs 46, 79 and 80.

⁽²⁾ See the judgment of the Court of 22 April 2015, *Klein v Commission*, C-120/14 P, ECLI:EU:C:2015:252, paragraph 71.

a risk to health or safety, to take measures 'to withdraw such devices from the market or prohibit or restrict their being placed on the market or put into service' and requires the Commission to verify whether such measures are justified, this Commission Decision relates to the measure taken by the French authorities to restrict the presence on the market of the device in question.

- (18) It is clear from the decision notified by the French authorities and from the consultations conducted with the interested parties that compliance with the essential requirements of the Directive concerning the risk/benefit ratio and minimising risk and the proper application of standards are being called into question.

2.1. Failure to comply with essential requirements

2.1.1. Essential requirements concerning the risk/benefit ratio

- (19) Section 1 of Annex I to Directive 93/42/EEC provides: 'The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will 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 when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety [...]'. Section 6 of Annex I to the Directive provides: 'Any undesirable side-effect must constitute an acceptable risk when weighed against the performances intended'.
- (20) As regards the risks, it should be pointed out at the outset that the risk caused by the ingestion of lead is widely documented, in particular in the publications cited by the 'Guideline for elemental impurities – Q3D' drawn up by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) ⁽¹⁾, in the 'Report on Carcinogens, fourteenth edition' of the U.S. Department of Health and Human Services, in the 'Scientific opinion on lead in food' of the European Food Safety Authority (EFSA) and in the publications cited by Commission Regulation (EC) No 1881/2006 ⁽²⁾. In the present case, the device contains lead and is intended to be ingested.
- (21) It should also be noted that the public is exposed to lead by many routes (air, water, food), with the result that any additional exposure, such as that caused by use of the device, increases the risk associated with exposure to lead.
- (22) Moreover, the French authorities refer to the 'Guideline for elemental impurities – Q3D' (hereinafter 'Guideline ICH Q3D'), drawn up by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), adopted by the European Medicines Agency (EMA) in December 2014 and applied by it to new applications for authorisation to place medicinal products on the market as of June 2016 and to existing authorisations for placing medicinal products on the market as of December 2017. This Guideline concerns elemental impurities in medicinal products, namely elements which do not provide any therapeutic benefit to the patient, with the result that their levels must remain within acceptable limits. It establishes a permitted daily exposure for elements of toxicological concern. For lead, the Guideline indicates that exposure to this element may cause neurological, reproductive, immune, cardiovascular and renal health effects; it establishes permitted daily exposure at 5 µg per day, irrespective of the route of administration.
- (23) The tests to which the French authorities refer show that the device contains levels of lead between 16 and 22,9 µg/g. A course of treatment involving six capsules of 335 mg per day (i.e. 2 g per day), as provided for in the instructions for use of the device, corresponds to an ingested amount of lead of between 32 and 46 µg per day, which is several times higher than the reference threshold of 5 µg per day.
- (24) With regard to use of Guideline ICH Q3D, it should be pointed out that this Guideline, while it applies formally to medicinal products, concerns the presence of elements (including lead) which do not provide any therapeutic benefit (elemental impurities) and which raise toxicological concerns in products administered orally, amongst other routes. It may therefore be considered relevant in assessing the risk associated with using a medical device which contains lead as an impurity and which is administered orally.

⁽¹⁾ Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, 'Toxicological profile for lead', 2007; National Toxicology Program, U.S. Department of Health and Human Services, 'Monograph on health effects of low-level lead', 2012.

⁽²⁾ Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs (OJ L 364, 20.12.2006, p. 5).

- (25) Finally, it should be pointed out that the manufacturer does not contest the fact that the device contains lead. Nor does the manufacturer contest the fact that lead is released by the device, albeit to a minor extent. Moreover, the manufacturer indicates that the risks identified by the reports cited by the French authorities — namely cardiovascular, neurological and nephrotoxic effects of lead in humans — were taken into account through the indications in the instructions for use of the device, in such a way that the essential requirement of Section 1 of Annex I to the Directive has been met; the manufacturer therefore acknowledges that use of the device poses risks, albeit at an acceptable level. In addition, a report from the NAMSA laboratory cited by the manufacturer acknowledges that there is a risk associated with the presence of lead in the device, while describing this risk as low.
- (26) It follows from the above that use of the device poses a risk to the health or safety of patients which the manufacturer is responsible for keeping within acceptable limits in relation to the benefits provided by the device.
- (27) As regards the benefits, according to the instructions for use, the device is intended to ‘prevent digestive problems, reduce digestive discomfort, restore digestive comfort and reduce abdominal circumference’. It should be pointed out that, in accordance with Article 1(2) of the Directive, a medical device is assumed to have a medical purpose. In the present case, it would seem that among the four claims made in the instructions for use, only the one relating to ‘preventing digestive problems’ could possibly be described as being medical in nature. In the absence of details in the instructions for use or technical documentation and in view of the other claims and the advertising for the device focusing on obtaining a ‘flat stomach’, it is fair to assume that the digestive problems in question are nothing out of the ordinary. All in all, the device appears to be of little benefit in medical terms.
- (28) In view of this, the French authorities were able to conclude that the device does not comply with the essential requirements of the Directive with regard to the risk/benefit ratio.
- (29) This conclusion is confirmed by the failure to comply with the essential requirement concerning clinical evaluation. Section 6a of Annex I to Directive 93/42/EEC provides: ‘Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X’. Section 1.1 of Annex X (clinical evaluation) to the Directive provides: ‘As a general rule, confirmation of conformity with the requirements concerning the characteristics and performances referred to in Sections 1 and 3 of Annex I, under the normal conditions of use of the device, and the evaluation of the side-effects and of the acceptability of the benefit/risk ratio referred to in Section 6 of Annex I, must be based on clinical data’.
- (30) In the present case, as regards the benefits, the device is intended to ‘prevent digestive problems, reduce digestive discomfort, restore digestive comfort and reduce abdominal circumference’, as indicated above. However, the conclusions of the clinical evaluation report prepared by the NAMSA laboratory at the manufacturer’s request ⁽¹⁾, and based on all the data available, state that three clinical claims were examined (‘reduces digestive discomfort, helps to reduce the circumference of the waist, allows digestive comfort to be rapidly improved’) and that only the two claims associated with reducing digestive discomfort and reducing the circumference of the waist are considered to be backed up by clinical data. The fourth claim associated with preventing digestive problems is not mentioned in the conclusions of this clinical assessment report. The manufacturer therefore did not provide clinical data to support the existence of all the beneficial effects claimed and in particular the existence of a beneficial effect in terms of preventing digestive problems. The assessment of the clinical data therefore does not confirm that the device complies with the essential requirement relating to the risk/benefit ratio.
- (31) In view of this, it was possible to conclude that the device does not comply with the essential requirement relating to the clinical evaluation, in connection with the essential requirement relating to the risk/benefit ratio.

2.1.2. Essential requirements relating to minimising risk

- (32) Section 7.2 of Annex I to Directive 93/42/EEC provides: ‘The devices must be designed, manufactured and packed in such a way as to minimise the risk posed by contaminants and residues to the persons involved in the transport, storage and use of the devices and to the patients, taking account of the intended purpose of the product. Particular attention must be paid to the tissues exposed and to the duration and frequency of exposure’. Section 7.5 of Annex I to the Directive provides: ‘The devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaking from the device. Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction, in accordance with Annex I to Council

⁽¹⁾ This report is entitled ‘Project 1 647 26 — Clinical evaluation report — Ventre plat devices — Version: V2 final May 24, 2016’.

Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances [...]. Annex I to Council Directive 67/548/EEC ⁽¹⁾ has become Part 3 of Annex VI to Regulation (EC) No 1272/2008 of the European Parliament and of the Council ⁽²⁾.

- (33) It follows from the above that use of the device poses a risk to the health or safety of patients (points 20-26), which it is the manufacturer's responsibility to reduce to a minimum. Moreover, lead is described as a substance toxic to reproduction in Part 3 of Annex VI to Regulation (EC) No 1272/2008; it is also considered to be a 'substance of very high concern' by the European Chemicals Agency (ECHA) ⁽³⁾, which justifies special attention being paid to it.
- (34) For the manufacturer of a medical device, the above-mentioned essential requirements may involve choosing batches of raw materials posing the least risk in terms of the toxic substances which they contain, i.e. verifying the concentration of a harmful substance in the batches of the raw material and selecting the batches showing a concentration which is compatible with the state of the art. In the present case, the raw material which forms part of the composition of the device, namely clay, contains harmful substances, in particular lead, in concentrations which may vary as it is a raw material of natural origin. The French authorities, like the Belgian authorities, have shown that there is a high degree of variation in the lead levels of different batches of capsules of the device. The manufacturer had the option of checking the lead content of the different batches of clay prior to manufacture and of selecting only those batches whose low lead content would have guaranteed that the capsules manufactured from this raw material contained a concentration lower than the threshold in Guideline ICH Q3D. However, under the contract between the manufacturer and its supplier, the batches of raw material were tested to determine their lead concentration and the manufacturer accepted batches whose lead concentration did not exceed 15 ppm, which equates to 15 µg/g. Given that a daily treatment of six capsules corresponds to 2 g, the quantity of lead ingested by patients could reach 30 µg per day, i.e. much more than the threshold of 5 µg per day. The manufacturer has therefore not reduced as far as possible the risk associated with the presence of lead in the device by selecting batches of raw material which would have made it possible to manufacture a device containing a level of lead below the threshold set by Guideline ICH Q3D.
- (35) The above-mentioned essential requirements may also lead the manufacturer of a device to select, from different raw materials, the one which poses the fewest risks as regards the toxic substances which it contains. Indeed, Section 7.1 of Annex I to the Directive provides that 'particular attention must be paid to the choice of materials used, particularly as regards toxicity [...]'. In the present case, other raw materials — such as, for example, activated charcoal, simeticone or dimeticone — have properties similar to clay and are likely to achieve the medical purpose claimed by the manufacturer for its device, namely 'to prevent digestive problems'. These other raw materials are not known to contain lead and are therefore unlikely to pose the risks associated with the device in question. The manufacturer did not, however, try to find an alternative raw material uncontaminated with toxic substances (see its email of 30 March 2018). It has therefore not reduced as far as possible the risk associated with the presence of lead in the device in this way.
- (36) In view of this, the French authorities were able to conclude that the device did not comply with the essential requirements of the Directive with regard to minimising risk.

2.1.3. *Objections raised by the manufacturer concerning failure to comply with essential requirements*

- (37) The manufacturer calls into question the use of Guideline ICH Q3D. It argues in particular that the Guideline is not applicable *ratione materiae* — it applies to medicinal products — and *ratione temporis* — it applies to new applications for authorisation to place medicinal products on the market as of June 2016 and to existing authorisations to place medicinal products on the market as of December 2017 — and that its application runs counter to the principles of legality and legal certainty.
- (38) However, use of Guideline ICH Q3D is in keeping with Article 8(1) of the Directive, which requires a Member State to take certain interim measures if it notices that a medical device poses a risk to safety and/or health, and which does not limit the information which the Member State may draw on to show that such a risk exists. Moreover, for the reasons mentioned above (point (24)), while being formally applicable to medicinal products, the Guideline is relevant in identifying the risk associated with the presence of lead in a medical device whose situation is similar to that of a medicinal product. It follows that use of the Guideline appears to have a legal basis and be predictable.

⁽¹⁾ OJ 196, 16.8.1967, p. 1.

⁽²⁾ Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures (OJ L 353, 31.12.2008, p. 1).

⁽³⁾ <https://echa.europa.eu/substance-information/-/substanceinfo/100.028.273>

- (39) The manufacturer calls into question the method used to evaluate the risk. It argues, in particular, that this method, based on the quantity of lead contained in the device, is not relevant in assessing compliance with the essential requirements which refer to substances released by a device and that it is not suitable for a device based on clay, which does not release its elements.
- (40) However, in the circumstances surrounding the present case, in the absence of an *in vivo* study making it possible to assess the quantity of lead actually released by the device, the method based on the quantity of the toxic substance contained in the device makes it possible to determine the quantity likely to be released into the body and thus to assess the risk posed by substances released by the device. It should also be pointed out, first, that the fact that the device releases a certain amount of lead is not disputed (as shown by tests carried out by the manufacturer itself) and, second, that while the manufacturer considers the amount of lead released to be small, the method used by the manufacturer to reach this conclusion is disputable (see points 47 et seq. below).
- (41) The manufacturer argues that even if Guideline ICH Q3D were used, the amount of lead released (which it assesses at 3,126 µg per day in its communication of 30 November 2016, and which is estimated at 3,96 µg per day in the report of February 2017 by the NAMS laboratory) would be below the threshold mentioned in Guideline ICH Q3D (which is 5 µg per day).
- (42) However, the method used by the manufacturer to determine the quantity of lead released by the device is disputable (see points 47 et seq. below) and therefore does not make it possible to tell whether the quantity determined using this method is so low that it does not pose a risk, taking into consideration Guideline ICH Q3D and other reference documents.
- (43) The manufacturer argues that the (cardiovascular, neurological and nephrotoxic) risks identified by the French authorities were taken into account through the indications the instructions for use of the device, with the result that the device complies with the essential requirement of Section 1 of Annex I to the Directive. It also argues that excessive exposure to lead may be avoided through measures taken by the manufacturer such as indications in the instructions for use, with the result that a measure taken by the authorities which, among other things, prohibits the device from being placed on the market and requires it to be withdrawn from the market, runs counter to the principle of proportionality.
- (44) However, the indications added to the instructions for use by the manufacturer restricting use of the device with regard to certain patients (children, pregnant women and individuals with kidney disease) do not eliminate the risk of lead poisoning for the population as a whole. An *in vivo* study showing that the quantity of lead actually released by the device is lower than the threshold indicated in the Guideline would help to eliminate the risk of excessive exposure to lead.
- (45) Article 8(1) of Directive 93/42/EEC takes the proportionality principle into account by providing that where a risk to the health and/or safety of persons is ascertained, appropriate interim measures must be taken to withdraw the devices in question from the market or prohibit or restrict their being placed on the market. It follows in the present case that where the French authorities show that a risk of this kind exists, a measure consisting in suspending the placing on the market of the device and withdrawing the device from the distributors until it is brought into line with the regulations is in keeping with Article 8(1) of the Directive and with the principle of proportionality.
- (46) In view of this, the objections raised by the manufacturer are not such as to call into question the French authorities' observation that the device does not comply with certain essential requirements of the Directive.

2.2. Incorrect application of standards

- (47) It follows from Article 8(1) of Directive 93/42/EEC that the risk requiring the Member States to take measures may result from the incorrect application of the standards referred to in Article 5 of the Directive which the manufacturer claims to have applied.
- (48) The manufacturer argues that the device was assessed and deemed compliant with certain harmonised standards concerning the biological evaluation of medical devices (in particular standards EN ISO 10993-1 2009/AC: 2010, EN ISO 10993-12 2012, EN ISO 10993-17 2009 and EN ISO 10993-18 2009), which correspond to certain essential requirements laid down in the Directive and a reference to which has been published in the *Official Journal of the European Union*, with the result that the device must be presumed to comply with the essential requirements in question.

- (49) These standards concerning the biological evaluation of medical devices provide in particular that the method used must reproduce the actual conditions of use of the medical device and that it may be necessary to conduct tests in addition to those described in the standards, as indicated by the provisions below.

- Standard EN ISO 10993-1 2010: biological evaluation of medical devices – evaluation and testing within a risk management process

The introduction to the standard states that ‘this approach combines the review and evaluation of existing data from all sources with, where necessary, the selection and application of additional tests, thus enabling a full evaluation to be made of the biological responses to each medical device, relevant to its safety in use’; that ‘biological testing is based upon, among other things, *in vitro* and *ex vivo* test methods and upon animal models’; that ‘it is not intended that ISO 10993 provide a rigid set of test methods, including pass/fail criteria’; that it must be used ‘taking into consideration all the factors relevant to the device, its intended use and the current knowledge of the medical device provided by review of the scientific literature and previous clinical experience’.

Point 4.4 of the standard states in particular that ‘the choice of tests and the data required in a biological evaluation, and their interpretation, shall take into account the chemical composition of the materials, including the conditions of exposure as well as the nature, degree, frequency and duration of exposure of the medical device or its constituents to the body, enabling the categorisation of devices to facilitate the selection of appropriate tests (...). The rigour necessary in the biological evaluation is principally determined by the nature, degree, duration and frequency of the exposure and the hazards identified for the material’.

Point 6.1 of the standard states in particular that ‘the results of the risk assessment can lead to the conclusion that additional material characterization is necessary, for example, where the margin of safety is not considered adequate if the entire amount of a particular chemical were to leach out. In such cases, appropriate extraction testing, simulating clinical exposure, can be used to estimate the degree of clinical exposure to the chemical constituent’.

Point 6.2.2 of the standard, concerning test descriptions, states in particular that ‘it is indispensable for testing that each device be considered on its own merits. Additional tests not indicated in the table [in Annex A] may be necessary’ (point 6.2.2.1), that ‘*in vivo* tests may be required to assess biodegradation of a material’ (point 6.2.2.13) and that ‘toxicokinetic studies shall be considered if (...) substantial quantities of potentially toxic or reactive degradation products and leachables are likely or known to be released from a medical device into the body during clinical use’ (6.2.2.14).

Annex A (informative) of the standard, which includes a table describing the biological evaluation tests to be taken into consideration with regard to the nature and duration of contact with the human body, does not explicitly cover ingestible medical devices. It states that ‘Table A.1 is a framework for the development of an assessment programme and is not a checklist’ and that ‘In addition to the framework set out in Table A.1, the following [i.e. the tests to be carried out] should be considered based on a risk assessment (...)’.

- Standard EN ISO 10993-12 2012: Biological evaluation of medical devices – Sample preparation and reference materials

Point 10.3.2 of the standard, which deals with extraction conditions and methods, indicates that it is necessary to ‘perform extraction using the appropriate extraction vehicle and time/temperature conditions to simulate exaggerated exposure wherever possible. Complete dissolution may be appropriate’.

Annex C (informative) of the standard, concerning the principles of test sample extraction, point C.1, indicates that ‘extraction conditions and application of the extract to test systems should therefore ideally reflect not only actual conditions of use of the products but also the purpose and predictability of the tests’ and that ‘biological tests are carried out to identify hazards and estimate the risks of the hazards occurring in exaggerated use and/or in actual conditions of use [...] exaggerated and exhaustive extraction is appropriate for hazard identification’.

- Standard EN ISO 10993-18 2009: Biological evaluation of medical devices – Chemical characterisation of materials

Point 5 of the standard states ‘However it is necessary to obtain information demonstrating the extent to which the constituents will be available under the actual conditions of use of the finished product to estimate the risk arising from them’.

- (50) In the present case it would appear that the manufacturer has used a testing method which does not reflect the actual conditions of use of the device. In particular, the method used to determine the quantity of lead released, which involves using an extraction volume of only 12 ml of water and using only acidified water without a bolus or an adequate (dynamic) environment, is not representative of the actual conditions of use of the device, namely ingestion with a greater quantity of liquid, the presence of a bolus and the progress of it all through the digestive tract. Moreover, it would appear that the manufacturer did not use another testing method, in particular tests in humans (*in vivo*), making it possible to determine the level of lead actually found in the bloodstream. It follows that the manufacturer does not show that the quantity of lead released is low and/or less than the reference threshold in Guideline ICH Q3D.
- (51) In view of this, it was possible to conclude that the standards referred to in Article 5 of the Directive, which the manufacturer claims to have applied, were incorrectly applied, with the result that the risk associated with the presence of lead in the device has not been ruled out.

2.3. Conclusion

- (52) Based on the information obtained from the decision notified by the French authorities, from the consultations conducted with the interested parties and in view of all the considerations above, the French authorities were able to conclude that the device may compromise the health and/or safety of persons and were thus able to adopt a provisional measure to ensure that the device is no longer placed on the market and is withdrawn from the market via the distributors,

HAS ADOPTED THIS DECISION:

Article 1

The measure adopted by the French authorities on 16 August 2016 regarding the Terrafor and Defiligne medical devices, in order to suspend their placing on the market and provide for the withdrawal of these devices from the market, is justified.

Article 2

This Decision is addressed to the Member States.

Done at Brussels, 25 October 2018.

For the Commission
Elżbieta BIENKOWSKA
Member of the Commission
