Agence nationale de sécurité du médicament et des produits de santé

Report

Market surveillance of PVC medical devices presented DEHP-free

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MARKET SURVEILLANCE OF PVC MEDICAL DEVICES PRESENTED DEHP-FREE (November 2015)

CONTENTS

Abbreviations

AFSSAPS	Agence française de sécurité sanitaire des produits de santé (French National Agency for Health Products Safety)
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé (French National Agency for Medicines and Health Products Safety)
ATBC	Acetyl tributyl citrate
BBP	Butylbenzyl phthalate
DBP	Dibutyl phthalate
DCHP	Dicyclohexyl phthalate
DEHA	Bis(2-ethylhexyl) adipate
DEHP	Di(2-ethylhexyl)phthalate
DEHT	Di(2-ethylhexyl) terephthalate
DEP	Diethyl phthalate
DIBP	Di-isobutyl phthalate
DIDP	Di-isodecyl phthalate
DINCH	Di(isononyl)cyclohexane-1,2-dicarboxylate
DINP	Di-isononyl phthalate
DIPP	Diisopentyl phthalate
DMEP	Di(2-methoxyethyl) phthalate
DMP	Dimethyl phthalate
DnOP	Di-n-octyl phthalate
DnPP	Di-n-pentyl phthalate
DPP	N-pentyl-isopentyl phthalate
MD	Medical devices
ppm	Parts per million
PVC	Polyvinyl chloride
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals (Regulation (EC) 1907/2006 of the European Parliament and of the Council of 18 December 2006, concerning the registration, evaluation and authorisation of chemicals and the restrictions applicable to these substances)
SVHC	Substance of very high concern
THF	Tetrahydrofuran
TOTM	Trioctyl trimellilate

1- BACKGROUND AND PURPOSE OF SURVEILLANCE

Phthalates, or phthalic esters, are a large family of chemical products, produced by esterification of a phthalic acid with one or several alcohols. Numerous phthalates are used as plasticisers and they are especially found in products made of polyvinyl chloride (PVC).

PVC is a plastic commonly used in medical devices, such as in infusion devices, extracorporeal circulation circuits (ECC), dialysis lines, respiratory circuits, feeding tubes, catheters (suction, vesical, endotracheal etc.), and blood bags.

Certain phthalates are classified in Europe as toxic to reproduction. This is the case especially of bis(2-ethylhexyl) (DEHP) which is classified as toxic to reproduction of category 1B according to Regulation (EC) 1272/2008[1].

DEHP is used in the manufacture of certain medical devices. When it is added to PVC, to make it more supple and flexible, DEHP does not bind covalently to the plastic matrix and may therefore migrate from the PVC to solutions or substances in contact with the PVC. Release may be promoted by certain factors such as contact with lipophilic substances.

European Directive 93/42/EEC, which provides a framework for medical device marketing, takes risks relating to substances released by a device into account specifically. The devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances released from the device. Use of a carcinogenic, mutagenic or toxic to reproduction (CMR) substance in a medical device should be closely monitored by manufacturer, according to requirement 7.5 of Annex I of the directive.
Since 21 March 2010, European Directive 2007/47/EC, amending Directive 93/42/EEC, requires labelling of certain medical devices containing phthalates whose carcinogenic, mutagenic or reprotoxic potential in humans is known or presumed, in order to better inform health care professionals The devices affected are those intended to administer, and/or remove, medicines, body fluids or other substances to or from the body, or devices intended for transport and storage of such body fluids or substances. Furthermore, if the intended use of such devices includes treatment of children or treatment of pregnant or nursing women, manufacturers are under the obligation to justify the use of these phthalates and to provide information on the residual risks for these groups of patients in the leaflet, and if applicable, on appropriate precautionary measures (see requirement 7.5 of Directive 93/42/EEC in full in Annex 1).

[1] Regulation (EC) 1272/2008, the CLP regulation, relates to the classification, labelling and packaging of substances and mixtures. This legislation classifies chemical substances into various categories of health hazard:

- Category 1A substances: substances known to have **carcinogenic and/or mutagenic and/or toxic to reproduction (CMR) potential for human**.
- Category 1B substances: substances presumed to have **CMR potential** for human.
- Category 2 substances: substances suspected to have **CMR potential** for human.

Before now, these hazard categories were defined by classification 1, 2 and 3 according to Directive 67/548/EEC (former categories 1, 2 and 3 are now categories 1A, 1B and 2 in Regulation (EC) 1272/2008 respectively).
Classified substances are listed in Annex VI, part 3 of the CLP regulation: table 3.1 lists the substances according to the CLP regulation and table 3.2 lists the substances according to Directive 67/548/EEC.

Amendments of this regulation are regularly published as adaptation to technical progress (ATP).

A specific symbol showing the presence of certain phthalates in medical devices was created and is described in harmonised standard NF EN 15986[2]. The symbol shall be accompanied by the abbreviated designation of the particular phthalate(s) used and set out in requirement 7.5 of the directive.

Given its toxicological profile and the evolution in legislation, several companies manufacture medical devices presented DEHP-FREE either by using plastic materials other than PVC, or by using PVC plasticised with plasticisers other than DEHP.
In 2012, in this context and with respect to marketing of PVC medical devices containing DEHP substitutes presented as being phthalate-free/DEHP-free, as part of its market surveillance missions coming under articles L.5311-1 and L.5311-2 of the French code of public health, the ANSM conducted a market surveillance relating to such medical devices. The purpose was to verify, by laboratory testing of the devices, manufacturers' claims as to the absence of phthalate or to the absence of DEHP more specifically in these medical devices.

In France, legal provisions prohibiting the use of certain medical devices containing DEHP were adopted so as to minimize exposure of certain populations of patients to DEHP in health care facilities. Law 2012-1442[3], article 3, provides for the prohibition, as of 1st July 2015, of the use of DEHP-containing tubing in paediatric, neonatology and maternity wards (see Annex 1). This provision, adopted in December 2012, is not discussed in this market surveillance.

2- METHODOLOGY

2.1. MEDICAL DEVICE SELECTION

2.1.1. CRITERIA FOR IDENTIFICATION OF THE MEDICAL DEVICES TO BE TESTED

The criteria for selecting the medical devices (MD) to be tested on the French market covered:

- **Use of the MD in specific medical procedures**: acknowledgement of the list of medical procedures with a potential for high exposure to DEHP put forward by the SCENIHR[4] in its 2008 report[5].
- **MD intended purpose**: MD types cited in requirement 7.5. of Directive 93/42/EEC, that is to say medical devices intended to administer and/or remove medicines, body fluids or other

[2] Standard EN 15986: 2011. Symbol For Use In The Labelling Of Medical Devices - Requirements For Labelling Of Medical Devices Containing Phthalates

[3] Law 2012-1442 of December 24, 2012 on the suspension of the manufacture, import, export and placing on the market of any food packaging containing bisphenol A. This law was published in the official journal of 26 December 2012.

[4] Scientific Committee on Emerging and Newly-Identified Health Risks.

[5] Opinion on the safety of medical devices containing DEHP-Plasticized PVC or other plasticizers on neonates and other groups possibly at risk, opinion adopted in 2008. This scientific opinion was updated in a report dated June 2015 by the SCENIHR "The safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups possibly at risk".

substances to or from the body, or devices intended for the transport and storage of such body fluids or substances.

- **MD composition**: devices (or parts) made of PVC containing plasticisers other than DEHP.

Therefore, 3 therapeutic areas in which PVC devices presented DEHP-free by several manufacturers were available on the French market during the product selection phase, were targeted during this market surveillance: **haemodialysis, enteral feeding and infusion.**

A dual approach was used to select device type by area to be tested. An approach focussing on the potential risk of DEHP release and a field-based approach on the use of these devices. It is in this context that several health care professionals were interviewed in order to more effectively target the choice of products to be tested.

Finally, concerning the choice of device references to be tested, devices used in paediatrics were searched first (where possible).

2.1.2. REVIEW OF SELECTED DEVICES

In order to select the devices, searches were made in the ANSM database, on manufacturers' websites and with health care professionals, and information requests or requests for confirmation about data on device ranges put to manufacturers by telephone or e-mail.
As part of market surveillance, 62 medical devices meeting the criteria above were selected. These devices are devices made by manufacturers with the intended purpose of administering fluids (medicinal products, nutrients or blood) to the body, and mainly include infusion, enteral feeding and haemodialysis as mentioned before:

- **Infusion**
  Extension sets / Tubes (16 MD)
  Infusion sets (7 MD)
  Transfusion sets (5 MD)
  Portable infusion pump (2 MD)

- **Enteral feeding**
  Enteral feeding tubes for pump or gravity system (14 MD)
  Nutrition feeding tubes (5 MD)
  Extension sets (2 MD)
  Extension set for gastrostomy button (1 MD)

- **Haemodialysis**
  Bloodlines (7 MD)

- **Others**
  Blood warming set (2 MD)
  Parenteral feeding tubes (1 MD)

2.2. SURVEILLANCE PROTOCOL

2.2.1. SAMPLE COLLECTION AND INFORMATION PROVIDED BY THE COMPANIES

Firstly, 27 companies marketing the medical devices in France were contacted by post. The list of the companies contacted can be found in Annex 2.

For each of the devices selected, the companies were asked to provide:

- 4 samples of the last finished product batch manufactured, for phthalate identification and quantification testing to be carried out at the ANSM's laboratory in Montpellier-Vendargues,
- Information: manufacturer's name, leaflet, labelling, technical sheet, plasticiser type, production site.

In total, 62 devices of 33 manufacturers (European and outside Europe) intended to be used in adults and/or paediatrics were received by the ANSM's laboratory.

The production sites of these products are located in Europe or outside Europe and the manufacturers cited various plasticisers in the composition of the products: TOTM, DEHT, DEHA, DINCH, ATBC and DINP.

Out of the 62 devices received, one was excluded from market surveillance as testing was difficult due to the presence of several plastics (PVC, polyethylene (PE) and ethylene-vinyl acetate (EVA)) in the tubing composition (PE making it impossible to dissolve the sample in tetrahydrofuran (THF), a necessary step in the testing process).

From the unit packaging and/or sales packaging labels provided by the companies for the 61 devices, the following was noted:

- presence of the symbol given in harmonised standard EN 15986[6] on the packaging of one device (confirmed by the manufacturer after investigation),
- 60 devices were not labelled as a phthalate-containing device. It was also noted that the labelling of 46 of the devices (77%) carried a claim stating the absence of phthalates or DEHP specifically, or a graphic representation designed by the manufacturer, possibly suggesting the absence of such substances, which is not provided for in the directive. A selection of the symbols observed can be found in Annex 3.

Also, as for the labelling and information provided with the device, the following should be specified for some devices:

- Following receipt of 2 arterial-venous blood line set references, the manufacturer informed the ANSM that DEHP was used as plasticiser in the device collection bag. The manufacturer justified the absence of labelling stating "Presence of DEHP" as the bag does not come into contact with the fluid. The collection bag is used when the extracorporeal circuit is rinsed (lines and dialyser) using physiological saline solution, before the start of treatment and therefore before connecting the patient. After rinsing the circuit, it is then disposed of and does not come into contact with the patient at any time.

[6] Standard EN 15986: 2011. Symbol For Use In The Labelling Of Medical Devices - Requirements For Labelling Of Medical Devices Containing Phthalates.

- For 2 devices, a DEHP limit was mentioned in the product leaflet:

    - For the device stating that it contains phthalates on the packaging, the leaflet states that "The tubing contains less than 0.2% DEHP plasticiser".
    - For another device not labelled (device itself or unit packaging) as a phthalate-containing device, the information "contains < 0.1% phthalates: DEHP. No added DEHP in the formula", features in the leaflet.

2.2.2. DEVICES TESTED

The devices received are more or less complex products, made up of several elements of different materials. The devices were tested in 2012 at the ANSM's laboratory for substances in these various elements. The various parts tested were therefore the PVC tubes, drip chambers, bubble traps and PVC bags. Elements for which the material was not stated were also tested. Nozzles, taps, connectors, clamps, rigid parts and parts made of a material other than PVC were not tested.
The devices received all comprised at least a tube which was routinely tested.

In total, 107 device parts were tested (1 to 7 parts tested per device according to complexity) at the ANSM's laboratory.

2.2.3. TEST METHOD

The medical devices were tested using a method developed and approved by the ANSM, which involved gas chromatography and mass spectrometry (GC/MS). The method chromatographic conditions are given in Annex 4.

The sample preparation method involved dissolution of a test sample from the part tested (tube, bag, drip chambers) in Tetrahydrofuran (THF) followed by PVC precipitation by addition of ethanol.

This method is used for identification and quantification of:

- category 1A or 1B CMR phthalates as per Regulation (EC) 1272/2008,

but also for identification of:

- phthalates no classified as CMR of category 1A or 1B as per Regulation (EC) 1272/2008,
- plasticisers currently used as alternative substances to DEHP in PVC medical devices.

The list of analytes can be found in Annex 5.

Two GC/MS chromatographic conditions were developed for the analysis:

- Condition 1 with a report limit fixed at 100 ppm (0.01%) for most of the analytes, among which 8 phthalates classified as toxic to reproduction of category 1B as per Regulation (EC) 1272/2008.

- Condition 2 with a report limit fixed at 500 ppm (0.05%) for DINP, DIDP and DINCH due to the presence of multiple isomers leading to a loss of sensitivity for these compounds (see Annex 5).

After later optimisations, this test method gave rise to a scientific article in the *Journal of Chromatography B*[7]. The principal optimisation consisted of pooling the 2 methods initially developed to test medical devices (one chromatographic analysis of plasticisers other than DINP, DIDP and DINCH and one chromatographic analysis for DINP, DIDP and DINCH) into one by increasing the report limit to 0.1% for DINP, DIDP and DINCH.

IN TOTAL:

- 33 manufacturers
- 61 medical devices tested
- 60 devices not labelled as phthalate-containing devices:
  - 46 labelled phthalate-free/DEHP-free
- 107 medical device parts tested:
  - 75 tubes, 26 drip chambers or bubble traps, 6 bags

3- LABORATORY TEST RESULTS

3.1. EXPRESSION AND COMMUNICATION OF THE RESULTS

An analysis report (AR) was issued to each of the companies for each of their medical devices. The AR accurately describes the parts of the device tested and provides detailed results for each part tested.

The results for the substances searched for and observed at a limit higher than their report limit are expressed in parts per million (ppm) and as a percentage w/w. The quantity of substance detected and the weight of the part tested are stated in each analysis report.

The results are summarised hereafter and remain anonymous.

3.2. IDENTIFICATION AND QUANTIFICATION OF CATEGORY 1A OR 1B CMR PHTHALATES

The primary objective of the test was to verify there was no category 1A or 1B CMR phthalates in the devices supposedly not containing them.

At the date of this market surveillance, 8 phthalates were classified as toxic to reproduction of category 1B (Repr.1B) according to Regulation (EC) 1272/2008: BBP, DBP, DEHP, DIBP, DIPP, DMEP, DnPP and DPP and none as category 1A[8].

[7] Gimeno P et al, J.Chromatogr.B 949-950 (2014) 99-108. Identification and quantification of 14 phthalates and 5 non-phthalates plasticizers in PVC medical devices by GC-MS.

[8] It should be noted that the list of substances classified under Regulation (EC) 1272/2008 is regularly updated: update of the substance classifications that already feature and/or inclusion of new classifications. Since the date of

These 8 phthalates were therefore searched for in the devices tested. The results as to their identification or non-identification in the parts tested are given below.

For 18 of the devices, around 30% of the devices tested, none of these 8 phthalates was detected at a concentration higher than the report limit set at 100 ppm (0.01%) for any of the parts in contact with the fluid tested.

As for the other 43 devices, BBP, DBP, DIBP, DIPP, DMEP, DnPP and DPP were not found at a concentration higher than their report limit. Therefore for these MD, only DEHP was detected among the CMR phthalates searched for, in at least one of the parts tested:

- for 32 of these devices, the concentration observed is between 100 (0.01%) and 1,000 ppm (0.1%) in one or several of the parts tested. Among these devices are the 2 devices especially for which a DEHP concentration limit was mentioned in the leaflet; the product test results are consistent with the information provided in the leaflet for these products,
- for 11 of these devices, the DEHP concentration measured is higher than 1,000 ppm (0.1%) in at least one part tested. Maximum DEHP concentration observed in the parts in contact with the fluid is 3.6%.

RESULTS

- Testing for 8 phthalates classified as a category 1B reprotoxic (Repr.1B)
- 18 MD: no Repr.1B phthalates detected
- 43 MD: DEHP found
  - 32 MD: 100 ppm < concentration observed < 1,000 ppm
  - 11 MD: concentration observed > 1,000 ppm

3.3. IDENTIFICATION OF SUBSTANCES OTHER THAN PHTHALATES CLASSIFIED AS CMR OF CATEGORY 1A OR 1B.

Secondarily to the main surveillance objective, the test method developed by the ANSM also offered the possibility to look for:

- Certain plasticisers, phthalic or non-phthalic compounds, used today as DEHP substitutes : DEHT, ATBC, DEHA, TOTM, DINCH and DINP.
- Other orthophthalic acid esters: DCHP, DEP, DIDP, DMP and DnOP.

These substances were not classified CMR according to Regulation (EC) 1272/2008 at the date of surveillance (see Annex 5).

Further to analysis of the 61 devices, the following was observed:

the market surveillance, new substances have been classified as CMR, this is the case of the phthalate "dihexylphtalate (cas no. 84-75-3)" which was classified as a Repr.1B in October 2013 (ATP 944/2013).

- The presence, in certain devices, of different plasticisers, depending on the parts of the device tested (i.e.: tube /drip chamber).

- TOTM was mainly used as plasticiser for around half the parts tested, followed by DINCH (16%) and DEHA (11%). Other plasticisers, ATBC, DEHT and DINP, and combination of 2 plasticisers were found in less than 10% of the parts tested respectively.

- For several devices, residual quantities of some of these substances not used as plasticiser (contaminants) at concentrations ranging up to 3,000 ppm in the parts tested. This was especially the case of DEHT which was found in most products (70%). DEHT, which is a terephthalate (terephthalic acid esterification product), is a DEHP structural isomer (orthophthalic acid ester) but does not have the same toxicity profile as the latter.

- Absence of detection of phthalates DCHP, DIDP, DMP and DnOP above the report limit set for these substances. DEP traces were found only once in a sample.

4- DISCUSSION / SURVEILLANCE FOLLOW-UP

The results on the substances searched for in the batches tested were forwarded to the companies. With regard to the results and to the non-compliances noted for a certain number of medical devices, as to the non-observance of requirement 7.5 of Annex I to Directive 93/42/EEC, an adversarial phase was undertaken with the companies. They informed the ANSM of action planned and of their own reading of this requirement.

4.1. IDENTIFICATION OF THE CAUSE OF DEHP PRESENCE IN THE DEVICES

Following detection of residual quantities of DEHP in their medical devices, several manufacturers conducted an investigation into the device manufacturing process and with raw material suppliers, in order to understand where the DEHP came from in the batches tested. The manufacturers said they used DEHP substitutes and did not add DEHP to the composition of device parts in contact with fluids, in accordance with their labelling which does not mention phthalates.

Following the investigations, the manufacturers provided several possible explanations, according to the DEHP concentrations observed in their devices, especially:

- it is present as an impurity possibly deriving from the alternative plasticiser manufacturing process,
- contamination during the MD manufacturing process,
- contamination during device packaging.

4.2. NOTION OF THRESHOLD VALUE FOR LABELLING REQUIREMENTS

The main point of discussion with the manufacturers concerned by the presence of DEHP detected in their products during market surveillance, was application or non-application of a threshold value with respect to the labelling requirements for medical devices containing category 1A or 1B CMR phthalates.

A large number of companies refer to Regulation (EC) 1907/2006 (REACH)[9] which sets a concentration limit of 0.1 % weight/weight, above which economic operators are required to provide information on the substances of very high concern[10] contained in the articles[11]. It should be noted that this limit value was set to enforce the requirement to provide information in order to ensure transmission of information within the supply chain for any articles coming under REACH, regardless of the type of material.

The claims made by the manufacturers as to the absence of phthalates/DEHP in their devices are therefore based on the declarations by their suppliers, who guarantee that their products do not contain DEHP according to the terms of the REACH regulation, at a concentration higher than 0.1% weight/weight.

Also, several manufacturers, according to their own interpretation of standard NF EN 15986, justify not having labelled their MD as phthalate-containing devices, as DEHP is not added to the PVC formulation, alternative substances having been used to replace this substance.

Directive 93/42/EEC, which is a sector-specific directive, does not provide a threshold value from which phthalate labelling is compulsory. According to requirement 7.5, the device should be labelled if parts of the device (or the device itself) contain category 1A or 1B CMR phthalates.

This directive is currently being revised as part of a draft regulation which proposes a threshold value of 0.1% for the labelling requirement for medical devices containing phthalates classified as category 1A or 1B CMR. This draft regulation is in a discussion stage at the date of drafting this report.

At the same time, discussions between Member States are currently ongoing in view of taking a joint position on the requirement relating to labelling of medical devices containing phthalates as set out in requirement 7.5 of the current directive.

Therefore, given the above, and pending adoption of a European position, ANSM has decided, despite the regulatory obligation provided for by the abovementioned essential requirement 7.5, not to take automatically a decision of sanitary police based principally or exclusively on the non-compliance of a labelling not stating the presence of phthalates classified as category 1A or 1B CMR for medical devices or parts of devices concerned by this requirement containing less than 0.1% mass by mass of the plasticised material.

When the “phthalate free” claim is used by the manufacturer for medical devices, these ones shall not contain any trace of phthalates. The presence of residual phthalate levels in the device, irrespective of the concentration, means that the device cannot be declared as a device that "does not contain phthalates".

[9] Regulation (EC) 1907/2006 of the European Parliament and of the Council of 18 December 2006, concerning the registration, evaluation and authorisation of chemicals and the restrictions applicable to these substances (REACH).

[10] Substance of very high concern, SVHC (art.57 of REACH). DEHP is a SVHC.

[11] Article according to REACH (art 3.3. REACH): means an object which during production is given a special shape, surface or design which determines its function to a greater degree than does its chemical composition.

4.3. ACTION TAKEN BY THE AGENCY

4.3.1. APPLICATION OF ESSENTIAL REQUIREMENT 7.5.

In the light of the detection of DEHP in their devices and in response to ANSM's request to companies to inform it of the measures to be taken, several manufacturers have taken corrective actions to reduce the presence of residual DEHP in their products.

This is especially the case of medical devices for which DEHP was observed at concentration over 1,000 ppm (0.1%) in at least one of the device parts tested. Therefore for most of these devices (8/11), the manufacturers have informed the ANSM of the corrective actions taken to limit the residual presence of DEHP in their devices, such as:

- setting up of an extrusion line for DEHP-free plasticised PVC extrusion to prevent the risk of contamination after passage of DEHP-containing tubes on the same extrusion line,
- tests by PVC suppliers in order to check DEHP concentration in their PVC presented DEHP-free , and the need for MD manufacturers to have the results of tests for detecting DEHP in PVC granules at receipt or a certificate stating DEHP concentration is less than 0.1%,
- change of plasticiser.

The ANSM did not issue any specific remarks as to these actions. The manufacturers were not asked to label the devices concerned as phthalate-containing devices, given the corrective actions planned.
For 3 other devices with DEHP concentration over 1,000 ppm (0.1%) in at least one of the device parts tested, the distributors said they had stopped distribution of these products.
As part of its prerogatives in the monitoring of compliance of medical devices, the ANSM is likely to carry out verifications or further surveillance in order to verify the compliance of the devices, especially in reference to requirement 7.5.

Finally, for medical devices in which DEHP was detected at concentrations lower than 1,000 ppm (0.1%), the manufacturers were not asked to label the devices affected as phthalate-containing devices with regard to what was already said in point 4.2. Some manufacturers nevertheless sought to minimise the risk of residual DEHP in their devices.

4.3.2. "PHTHALATE FREE" LABELLING

Among the devices in which DEHP was detected, many of them carried a claim as to the absence of phthalates, or DEHP more specifically, on the device label.
These companies were asked to remove any claims or symbols suggesting the absence of phthalates from the device label, leaflet, or any non-promotional or advertising documents.

5- CONCLUSION

Medical devices (or parts of these devices) intended to administer and/or remove medicines, body fluids or other substances to or from the body, or devices intended for transport and storage of such body fluids or substances, containing phthalates classified as category 1A and 1B CMR according to Regulation

(EC) 1272/2008, must be labelled as phthalate-containing devices in accordance with requirement 7.5 of Directive 93/42/EEC, Annex I.

During market surveillance, and after sampling, which covered a certain number of medical devices in France intended by the manufacturer to be used to administer medicines, body fluids or other substances to the body, ANSM observed that a large number of these devices in which DEHP was not added as plasticiser, actually contained residual quantities of DEHP, without being labelled as a phthalate-containing device, despite the regulatory obligation provided for by the above mentioned essential requirement 7.5.

Indeed, the surveillance results demonstrated the presence of DEHP in around 70 % of the devices tested, with however, concentrations lower than 1,000 ppm (0.1%) being observed for most of them.
Compared to the residual quantities observed, impurities or contaminants, it should be recalled that when DEHP is used as plasticiser in devices made of PVC, its concentration in the plasticised PVC is often around 30 % to 40%.

This absence of labelling results from differences in interpretation of the labelling obligation set out in requirement 7.5 of Directive 93/42/EEC.

Therefore, considering the European context and the discussions between the Member States, in particular on the requirement relating to the labelling of medical devices containing certain phthalates as set out in requirement 7.5 of the applicable directive, ANSM has decided, at this time, not to take automatically a decision of sanitary police based principally or exclusively on the non-compliance of a labelling not stating the presence of phthalates classified as category 1A or 1B CMR for medical devices or parts of devices concerned by this requirement containing less than 0.1% mass by mass of the plasticised material.
ANSM will, however, carry out reinforced and precise surveillance of MDs affected, and of course reserves the right to exercise its policing powers in this area at any time and in accordance with the abovementioned provisions.

It should be specified that this does not exempt the manufacturer from reducing the presence of phthalate traces in the device to the lowest level possible, and reducing the risks resulting from the substances released.

Claims or symbols as to the absence of phthalates in the device were also often noted during surveillance on the labels of the products tested.

It is essential that all medical devices have the characteristics announced. A "phthalate-free" claim is not compatible with the presence of residual levels of phthalates in the device, irrespective of the concentration. This claim cannot therefore be applied to the labelling, instruction leaflet or any other information document, promotional or otherwise, if phthalates are present in even residual amounts.

The ANSM asked the manufacturers concerned to change the labelling for the devices tested.

Also, in a more comprehensive approach to market surveillance of medical devices, and in view of the potential presence of traces of DEHP in devices presented DEHP-free, manufacturers' attention is drawn to the need to take this information into account in their risk analysis and management system, and to

ensure that requirements to which the device is subject are met through the company's quality system. The manufacturer should implement the means necessary for:

- ensuring that purchased raw materials and materials conform to specified purchase requirements; the set specifications should include a requirement for category 1A or 1B CMR phthalates,
- preventing any risk of contamination by these substances during the various medical device manufacturing process steps, including packaging.

The attention of manufacturers is therefore drawn to the need to ensure the consistency of the information indicated on the labelling of their devices with respect to the presence of phthalates in view of the above.

Following the observations made during market surveillance, a notice to manufacturers on labelling of phthalate-containing medical devices will be published on the ANSM's website.

Finally, the ANSM continues market surveillance of DEHP-free medical devices and may be brought to conduct other actions so as to verify the compliance of devices marketed in France with requirement 7.5.

ANNEX 1 :

Phthalates and medical devices: REGULATORY BACKGROUND

EUROPEAN REGULATORY FRAMEWORK

1) <u>Directive 93/42/EEC amended by Directive 2007/47/EC</u>:

<u>With regard to article 28 of Directive 2007/47/EC:</u>
"Many Member States have established recommendations with the aim of reducing or limiting the use of medical devices containing critical phthalates on children, pregnant and nursing women and other patients at risk. To enable medical professionals to avoid such risks, devices which possibly release phthalates to the body of the patient should be labelled accordingly".

<u>Essential requirement 7.5 of Annex I to Directive 93/42/EEC:</u>

"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 should be given to substances which are carcinogenic, mutagenic or toxic to reproduction in accordance with Annex I to Council 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.

If parts of a device (or a device itself) intended to administer and/or remove medicines, body liquids or other substances to or from the body, or devices intended for transport and storage of such body fluids or substances, contain phthalates which are classified as carcinogenic, mutagenic or toxic to reproduction, of category 1 or 2, in accordance with Annex I to Directive 67/548/EEC[12], <u>these devices must be labelled on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging as a device containing phthalates.</u>
If the intended use of such devices includes treatment of children or treatment of pregnant or nursing women, <u>the manufacturer must provide a specific justification for the use of these substances with regard to compliance with the essential requirements, in particular of this paragraph, within</u> the technical documentation and within the instructions for use, information on the residual risks for these patient groups and, if applicable, on <u>appropriate precautionary measures</u>".

2) <u>Draft regulation revising Directive 93/42/EEC, proposal by the European Commission made public on 26/09/2012</u>:

<u>ANNEX I "General safety and performance requirements", requirement 7.4. :</u>

[12] Directive 67/548/EEC has since been replaced by Regulation (EC) 1272/2008. Categories 1 and 2 from the directive now correspond to categories 1A and 1B of this regulation respectively.

The devices shall be designed and manufactured in such a way as to reduce as far as possible and appropriate the risks posed by substances that may leach or leak from the device. Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction, in accordance with Part 3 of Annex VI to regulation (EC) N° 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) N° 1907/2006, and to substances having endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health and which are identified in accordance with the procedure set out in Article 59 of Regulation (EC) N° 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Registration of Chemicals (REACH).

If devices, or parts thereof, that are intended
– to be invasive devices and to come into contact with the body of the patient for short- or long-term, or
– to (re)administer medicines, body liquids or other substances, including gases, to/from the body, or
– to transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body

contain, in a concentration of 0.1% by mass of the plasticised material or above, phthalates which are classified as carcinogenic, mutagenic or toxic to reproduction of category 1A or 1B in accordance with Part 3 of Annex VI to Regulation (EC) No1272/2008, these devices shall be labelled on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging as devices containing phthalates. If the intended use of such devices includes treatment of children or treatment of pregnant or nursing women, the manufacturer shall provide a specific justification for the use of these substances with regard to compliance with the general safety and performance requirements, in particular of this paragraph, within the technical documentation and, within the instructions for use, information on residual risks for these patient groups and, if applicable, on appropriate precautionary measures."

FRENCH LAW

Extract from French law 2012-1442 of 24 December 2012 on the suspension of the manufacture, import, export and placing on the market of any food packaging containing bisphenol A (Official Journal of 26 December 2012):

Article 3
Heading I, tome II, part five of the French code of public health is completed by chapter IV as follows:

CHAPTER IV **"Prohibition of certain materials in medical devices"**

Art. L. 5214-1. **– From 1 July 2015, the use of tubing containing di (2-ethylhexyl) phthalate is prohibited in paediatrics, neonatology and maternity wards.**

Article 4

The Government presents a report on endocrine disruptors to the Parliament, within one year of enactment of this law. This report describes the health and environmental consequences of the increasing presence of endocrine disruptors in the diet, in the direct environment, in medical devices and in the human body. It especially studies the possibility of prohibiting the use of di (2-ethylhexyl) phthalate, dibutyl phtalate and butyl benzyl phthalate in all medical devices given that safer replacement materials are available.

ANNEX 2

Manufacturers and distributors concerned

Companies submitting devices: distributors or manufacturers	Manufacturers
ASEPT INMED, France	ASEPT INMED s.a., France
	LEVENTON, Spain
BARD, France	BARD ACCESS SYSTEMS, Inc, USA
BAXTER, France	BAXTER, Switzerland
	MEDICA S.p.A, Italy
B.BRAUN, France	B.BRAUN AG, Germany
BECTON DICKINSON, France	BECTON DICKINSON Infusion therapy AB, Sweden
BEXEN	OIARSO MK CO., PRC
	OIARSO S.COOP, Spain
CAIR LGL France	CAIR LGL France
CODAN, France	CODAN GmbH & Co, Germany
COVIDIEN, France	KENDALL, division of the TycoHealthcare Group LP, USA
	TycoHealthcare, Ireland
	SENDAL S.A., Spain
DORAN INTERNATIONAL, France	DORAN INTERNATIONAL, France
EUROMEDIS, France	EUROMEDIS, France
FRESENIUS KABI FRANCE, France	FRESENIUS KABI AG, Germany
FRESENIUS MEDICAL CARE, France	FRESENIUS MEDICAL CARE AG & Co.KGaA, Germany
FRESENIUS VIAL, France	FRESENIUS KABI AG, Germany
GAMBRO, France	GAMBRO DASCO S.p.A Italy
GROUPE DIDACTIC, France	GROUPE DIDACTIC, France
HOSPAL, France	GAMBRO DASCO S.p.A Italy
HOSPIRA, France	HOSPIRA, Inc, USA
MACOPHARMA, France	MACOPHARMA, France
MEDWIN, France	MEDWIN, France
3M France, France	3 M Health Care, U.S.A.
NUTRICIA, France	NUTRICIA Medical Devices B.V., Netherlands
SEGAP, France	PENTAFERTE S.p.A, Italy
SMITHS MEDICAL France	SMITHS MEDICAL, U.S.A.
	S.O.F.A.P., Tunisia (Agent: OBELIS S.A., Belgium
SENDAL, France*	SENDAL, Spain
	WELL LEAD MEDICAL Co.Ltd, PRC
	SHANDONG QIAOPAI GROUP Co., Ltd, China
	NANTON EXCEED MEDICAL APPLIANCES Co., Ltd, China
VYGON France	VYGON France
WYM France	WOO YOUNG MEDICAL Co, Ltd

*This company no longer exists. The Sendal Group was bought out by the CareFusion group

ANNEX 3

Summary of the various symbols observed on the labels of devices tested

Labelling indicating absence of phthalates is not a requirement of the directive. There are no symbols set out in any standards to indicate "does not contain phthalates". Details on the use of negation of symbols are provided in Annex B (informative annex) of standard NF EN 15986.
However, different graphic representation were used by manufacturers on the labelling of their devices to indicate the absence of phthalates (or more specifically DEHP), in the devices. A summary of the different symbols observed during market surveillance is given below.

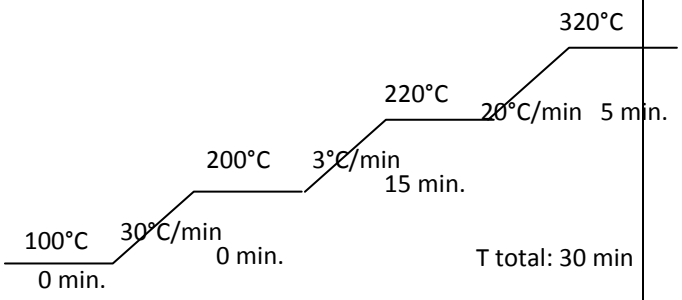
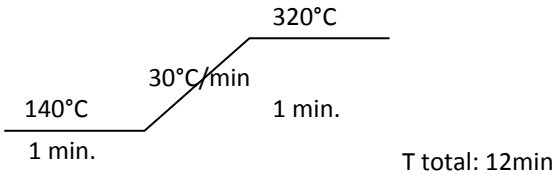
1. Use of the symbol described in standard NF EN 15986 (indicating presence) but with a large “X” placed over the symbol:

2. Other types of symbols used:

Remark: the symbol of a circle with a diagonal bar is the general prohibition symbol (see Annex B to standard NF EN 980).

ANNEX 4

ANSM test method: chromatographic conditions

Test type	CG/SM	
Apparatus	CG – VARIAN 3800 SM – VARIAN 1200 VARIAN 8400 automatic liquid injector (or equivalent)	
Column	VF-5MS (5%-Phenyl)-95%-dimethylpolysiloxane, 30 m x 0.25 mm x 0.25 µm (or equivalent)	
Conditions 01 CG		
Conditions 02 CG Sample re-injection		
T°C injector	300°C	
T°C interface	250°C	
T°C source	230°C	
Test time	30 min	
Carrier gas / flow rate	He / 1 ml/min	
Injector type	Liquid injector split / splitless	
Injection parameters:	<u>Conditions 01</u> 1 µL Injection at constant pressure Split 1/20th	<u>Conditions 02</u> 2 µL Injection at constant pressure Split 1/10th
Detection type	Single quadripole	
Ionisation mode	EI (70eV)	
Tune settings	Auto tune	
Analytical conditions (Full/SIR)	Full-scan identity testing (m/z 40-350) SIR assay on 3 ions specific to each compound (1 quantifying ion + 2 qualifying ions (with known ratio).	
Internal standard	4,4-Dibromodiphenyl	
Calibration range	0.25-5.0 µg/ml	
Solvent	Ethanol (injection)	

ANNEX 5:

Substances which have been searched for (Analytes)

French name *(English)*	**Abbreviation**	**CAS no.**	**CLASSIFICATION** according to Annex I to Directive 67/548/EEC [3]	**CLASSIFICATION** according to amended Regulation (EC) 1272/2008 [4]
Phtalate de butyle et de benzyle *(Butylbenzyl phthalate)* [1]	BBP	85-68-7	Category 2 reprotoxic	Repr.1B (Regulation 1272/2008)
Phtalate de dibutyle *(Dibutyl phthalate)* [1]	DBP	84-74-2	Category 2 reprotoxic	Repr.1B (Regulation 1272/2008)
Phtalate de bis(2-éthylhexyle) *(Di(2-ethylhexyl)phthalate)* [1]	DEHP	117-81-7	Category 2 reprotoxic	Repr.1B (Regulation 1272/2008)
Phtalate de di-isobutyle *(Di-isobutyl phthalate)* [1]	DIBP	84-69-5	Category 2 reprotoxic	Repr.1B (Regulation 790/2009)
Phtalate de di-isopentyle *(Diisopentyl phthalate)* [1]	DIPP	605-50-5	Category 2 reprotoxic	Repr.1B (Regulation 1272/2008)
Phtalate de di(2-methoxyéthyle) *(Di(2-methoxyethyl) phthalate)*[1]	DMEP	117-82-8	Category 2 reprotoxic	Repr.1B (Regulation 1272/2008)
Phtalate de dipentyle *(Di-n-pentyl phthalate)* [1]	DnPP	131-18-0	Category 2 reprotoxic	Repr.1B (Regulation 1272/2008)
Phtalate de N-pentyl-isopentyle *(n-pentyl-isopentyl phthalate)* [1] - Mélange d'isomères (DiPP, DnPP et DPP)	DPP	84777-06-0	Category 2 reprotoxic	Repr.1B (Regulation 1272/2008)
Citrate tributylique d'acétyle *(acetyl tributyl citrate)* [1]	ATBC	77-90-7	-	-
Phtalate de dicyclohexyle *(dicyclohexyl phthalate)* [1]	DCHP	84-61-7	-	-
Adipate de bis (2-éthylhexyle) *(Bis(2-ethylhexyl) adipate)* [1]	DEHA	103-23-1	-	-
Téréphtalate de bis(2-éthylhexyle) *(Di(2-ethylhexyl) terephthalate)*[1]	DEHT	6422-86-2	-	-
Phtalate de diéthyle *(Diethyl phthalate)* [1]	DEP	84-66-2	-	-
Phtalate de di-isodécyle *(Di-isodecyl phthalate)* [2]	DIDP	26761-40-0	-	-
Cyclohexane dicarboxylate de diisononyle *(di(isononyl)cyclohexane-1,2-dicarboxylate)* [2]	DINCH	166412-78-8	-	-
Phtalate de di-isononyle *(di-isononyl phthalate)* [2]	DINP	68515-48-0	-	-
Phtalate de diméthyle *(Dimethyl phthalate)* [1]	DMP	131-11-3	-	-
(*di-n-octyl phthalate)* [1]	DnOP	117-84-0	-	-
Trioctyl trimellilate [1]	TOTM	3319-31-1	-	-

[1] Report limit set at 100 ppm (0.01%)

[2] Substance looked for but not assayed (report limit set at 500 ppm (0.05%))

[3] Classifications listed in table 3.2, part 3 of Annex VI to Regulation (EC) 1272/2008

[4] Repr.1B: toxic to reproduction of category 1B. Annex VI to Regulation (EC) 1272/2008, part 3, table 3.