National Institute
for Public Health
and the Environment

Report 360050014/2009

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Continuous cycle of improvement of medical devices

A questionnaire on experiences and procedures

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This investigation has been performed by order and for the account of the Dutch Health Care Inspectorate, within the framework of V360050 ‘Supporting the Health Care Inspectorate on Medical Technology’

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Abstract

Continuous cycle of improvement of medical devices
Results of a questionnaire on experiences and procedures

Manufacturers of medical devices shall continuously monitor users' experiences in order to minimize any risk associated with their products. In practice, this does not take place sufficiently, which could jeopardize the safety of patients and users. This was the conclusion of an investigation performed by the Dutch National Institute for Public Health and the Environment (RIVM) and commissioned by the Dutch Health Care Inspectorate.

For this investigation, manufacturers were requested to complete a questionnaire on how they continuously work towards improving their products and to submit procedures relating to this cycle. The investigation concerned manufacturers of infusion pumps and washer disinfectors for flexible endoscopes – which are used for internal examinations. Furthermore, manufacturers of new medical devices involved in clinical investigations, e.g. stents (miniature mesh tubes to keep blood vessels open), were also included in the investigation.

Before a manufacturer places a medical device on the market, all possible risks related to the device must be analyzed and suitable measures taken to eliminate or reduce these risks. After the device has been placed on the market, the manufacturer shall continue to systematically review whether the risk estimation and the control measures taken are still acceptable or whether they need to be adjusted. This procedure for monitoring users' experience with a device was found to vary from an insufficient passive complaint procedure to an optimal active procedure including patient follow-up. Based on the users' experiences, inadequacies regarding the device itself or its instructions for use can be detected and then be acted upon.

One shortcoming that was found to occur frequently was the lack of a new risk assessment following the revision of a medical device. This review of the risk assessment is a crucial part of the process because product revision can introduce new risks.

Key words:
medical device, Medical Devices Directive, post-market surveillance, vigilance, risk management

Rapport in het kort

Continue cyclus voor verbetering van medische hulpmiddelen
Resultaten van een enquête over ervaringen en procedures

Fabrikanten van medische hulpmiddelen dienen voortdurend ervaringen van gebruikers te inventariseren om risico's van hun producten te verminderen. Op essentiële onderdelen gebeurt dit echter onvoldoende, waardoor de veiligheid van patiënten en gebruikers in het gedrang kan komen. Dit blijkt uit onderzoek van het RIVM in opdracht van de Inspectie voor de Gezondheidszorg.

Voor het onderzoek hebben fabrikanten enquêtes over deze continue cyclus van productverbetering ingevuld en procedures over onderdelen hiervan verstrekt. Het betrof fabrikanten van infuuspompen en van desinfecterende wasmachines voor flexibele endoscopen voor inwendig onderzoek. Daarnaast zijn ook fabrikanten aangeschreven, waarvan nieuwe hulpmiddelen werden geëvalueerd in een klinische studie, waaronder stents (kleine, gaasachtige buisjes die bloedvaten openhouden).

Voordat fabrikanten een hulpmiddel op de markt brengen moeten zij de risico's van het hulpmiddel in kaart brengen en maatregelen nemen om risico's uit te sluiten of te beperken. Na de introductie op de markt dienen zij systematisch en herhaaldelijk na te gaan of de risico-inschatting en maatregelen nog acceptabel zijn, dan wel moeten worden bijgesteld. Deze procedure voor het verzamelen van ervaringen met hulpmiddelen bleek te variëren van een onvoldoende 'passieve' klachtenprocedure tot een adequate werkwijze waarin patiënten 'actief' worden gevolgd. De ervaringen kunnen inzicht geven in onvolkomenheden van het hulpmiddel of van de gebruiksaanwijzing, die vervolgens kunnen worden opgeheven.

Een veelvuldig geconstateerde tekortkoming in dit proces is dat na een aanpassing van het medische hulpmiddel geen nieuwe risico-inschatting wordt gemaakt. Deze koppeling is cruciaal omdat productaanpassingen nieuwe risico's met zich mee kunnen brengen.

Trefwoorden:
medisch hulpmiddel, Richtlijn medische hulpmiddelen, post-market surveillance, vigilantie, risicomanagement

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Summary

Major shortcomings were observed for the continuous cycle of product improvement as implemented by manufacturers of medical devices. This was the outcome of a study performed by the Dutch National Institute for Public Health and the Environment. Before placing a medical device on the market, a manufacturer has to analyze, evaluate and control the risks related to the use of the device. After introduction of the device, the manufacturer shall repeatedly and systematically verify whether the risk evaluation and measures taken are still adequate or whether additional measures are required.

In order to assess the implementation of the continuous cycle of product improvement, manufacturers of infusion pumps, of flexible endoscope washer disinfectors and of medical devices used in clinical investigations were requested to complete a questionnaire and to submit applicable procedures on post-market surveillance (PMS) and notifying the competent authorities of incidents (vigilance).

The response rate of the manufacturers was high. From 33 manufacturers included in this study, 32 submitted information. The response was positively influenced by instantly reminding manufacturers when the submission deadline was exceeded, as 76 % of the included manufacturers needed to be reminded.

A crucial element of the continuous cycle, the update of the risk analysis following modification of a medical device, was not always implemented. This link is crucial as product modification can introduce new risks.

Furthermore, the procedural implementation of post-market clinical follow-up, e.g. extended follow-up of patients enrolled in pre-market clinical investigation, was not addressed by a majority of the included manufacturers. This is remarkable, as part of the manufacturers will perform post-market clinical follow-up for patients treated during the clinical investigation.

Risk management activities and corrective and preventive actions (CAPA) were underexposed in PMS and vigilance procedures. In several of the procedures assessed, both risk management activities and CAPA were not mentioned or referred to. Both activities are, however, crucial elements in the continuous cycle of product improvement. Moreover, approximately 40 % of the procedures did not describe active forms of surveillance. A proactive approach should be used to observe trends which can help manufacturers to improve user/patient satisfaction and to identify opportunities for device improvement.

Findings based on device experiences gathered from clinical investigations and PMS activities led to modification of medical devices in half or more of the cases, whereas vigilance activities resulted in device modifications in 25 % of the cases.

A substantial part of the manufacturers had not revised their procedure for more than two years, suggesting a rather static system of procedure management. When previous and current procedures were available, these were compared. In general, procedure revision did not lead to a substantial improvement of the contents of PMS and vigilance procedures, despite recent related changes in the regulation and guidance documents (so-called MEDDEV documents). It is recommended that manufacturers bring their vigilance procedure in line with the current MEDDEV guideline.

The findings of this investigation indicated that the cycle for continuous improvement has not been fully implemented by these manufacturers, which might have implications for patient safety. We feel that manufacturers, notified bodies and competent authorities could learn valuable lessons from these results when setting up, respectively auditing quality management systems.

1 Introduction

The continuous cycle of product improvement by manufacturers is an important aspect of the Medical Devices Directive (MDD) [1]. A model of this cycle is depicted in Figure 1. In order to guarantee the safe application of medical devices, the associated risks need to be managed. In the standard EN ISO 14971 'Medical devices – Application of risk management to medical devices', the process of risk management is defined as the systematic application of management policies, procedures and practices to the tasks of analysing, evaluating and controlling risk [2].
In selecting the most appropriate solutions for the design and construction of the devices, the manufacturer must apply the following principles in the following order, taking account of the generally acknowledged state-of-the-art [1]:

1. eliminate or reduce risks as far as possible (inherently safe design and construction);
2. where appropriate, take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated;
3. inform users of the residual risks due to any shortcomings of the protection measures adopted.

Risk management is a continuous process, described as a set of repeatable steps throughout the entire life cycle of medical devices. It is important to realize that deciding on risk acceptability is an ongoing, iterative process. Once new information becomes available, for example in the post-production phase, the acceptability of risk should be re-evaluated.

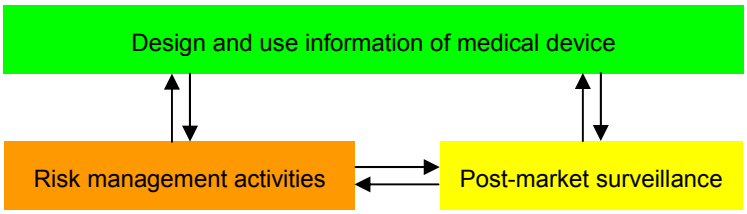

Figure 1. Continuous cycle of product improvement

The MDD requires the manufacturer of medical devices to 'institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase, including the provisions referred to in Annex X, and to implement appropriate means to apply any necessary corrective action. This undertaking must include an obligation for the manufacturer to notify the competent authorities of […] incidents immediately on learning of them' [1]. This procedure is usually termed post-market surveillance (PMS). Moreover, the provisions in Annex X requires that 'the clinical evaluation and its documentation must be actively updated with data obtained from the post-market surveillance. Where post-market clinical follow-up as part of the post-market surveillance plan for the device is not deemed necessary, this must be duly justified and documented'. Post-market clinical follow-up has not been defined in the MDD, but European guidelines introduced the expression in 2004 to promote a common approach for manufacturers and notified bodies to fulfil the requirements [3].
The monitoring and evaluation of incidents and mandatory notification of incidents to competent authorities is known as the medical devices vigilance system [4].
PMS activities thus imply the systematic collection, analysis, and interpretation of experiences of medical devices in relation to the generally accepted state-of-the-art. Subsequently, the results of PMS

activities have to be fed back into the risk management process. If necessary, this will lead to changes in the device design, protection measures and/or user information.
In the past years, the Dutch National Institute for Public Health and the Environment (RIVM) has performed several investigations into the quality of technical documentation of medical devices, as prepared by the manufacturers to prove that they comply with regulatory requirements [5-8]. These investigations indicated that there are major shortcomings in different parts of the continuous cycle of product improvement, such as risk analyses, user information and PMS procedures.
To gain an insight into the current implementation of the continuous cycle of product improvement, RIVM, in close cooperation with the Dutch Health Care Inspectorate, performed an investigation. Preliminary results of this investigation [9] were published previously and were integrated in the State of Health Care Report 2008 [10].

2 Methods

2.1 Selection of manufacturers and medical devices

In close collaboration with the Dutch Health Care Inspectorate, three medical device categories were selected for inclusion in this investigation:

- *Medical devices intended for clinical investigation*
  Eighteen manufacturers sponsoring clinical investigations (i.e., pre-market studies) with medical devices were included based on a previous RIVM investigation conducted in 2005-2006 [6]. One manufacturer sponsored two clinical investigations with two different medical devices. Thus, nineteen medical devices were selected. Although this product category consisted of various medical devices, the majority of manufacturers (15/18) were developing (cardio)vascular medical devices, such as stents, catheters, vascular prostheses, and heart valve prostheses;
- *Infusion pumps*
  Eleven manufacturers were included based on a previous RIVM investigation conducted in 2006 [8]. All infusion pumps were marketed in the Netherlands;
- *Endoscope washer disinfectors*
  Six manufacturers of endoscope washer disinfectors were included based on a RIVM investigation conducted in 2008 [11]. All manufacturers marketed their endoscope washer disinfectors in the Netherlands.

2.2 Data collection

In February 2008, the Dutch Health Care Inspectorate sent a letter to all manufacturers requesting submission of a completed questionnaire and surveillance procedures. Within one week after receipt of the letter, manufacturers were asked to provide the contact details of the person in charge of supplying the requested information. The questionnaire and procedures had to be returned within three weeks, preferably by e-mail, to the RIVM. The RIVM checked whether all documents were submitted. If manufacturers failed to submit questionnaire and/or procedures, contact persons were reminded instantly by the Health Care Inspectorate using the supplied phone and e-mail details.

2.2.1 Questionnaire

The questions in the questionnaire (see Appendix I for full questions) addressed whether:

- the medical device was CE-marked and released onto the market (for the product category including medical devices intended for clinical investigation);
- the medical device has been modified since the start of the clinical investigation or during the last two years, including the label and instructions for use as labelling is considered to be an integral part of the design of the medical device;
- the risk analysis has been updated since the start of the clinical investigation or during the last two years;
- experiences gained from the actual use of devices were collected and evaluated, i.e. pre-market and, where appropriate, post-market experiences.

2.2.2 Surveillance procedures

Along with the questionnaire, manufacturers were requested to submit their current PMS and vigilance procedures. Some manufacturers supplying medical devices intended for clinical investigation stated that their medical devices were not (yet) on the market and therefore no PMS and vigilance activities were required. Internet searches (i.e., scanning of manufacturers' websites) were performed to examine whether manufacturers had other CE-marked medical devices. If the result of the search was negative, i.e. no CE-marked medical devices, manufacturers did not have to submit PMS and vigilance procedures.

2.3 Data extraction

Data were extracted from the questionnaire for each medical device as well as from the procedures of each manufacturer. The questionnaire consisted of closed-ended as well as open-ended questions. As respondents were expected to answer questions in their own words, codes were assigned to categories of responses. Data extraction from current PMS and vigilance procedures was limited to the presence of essential procedure items (see Appendix II). Similarly, data were extracted from PMS and vigilance procedures, which were requested in previous RIVM investigations.
Data extraction was performed by two assessors. The results were compared and inconsistencies resolved. Data were entered manually in an electronic form using SPSS Data Entry Builder (SPSS Inc., Chicago, IL, USA). Before doing further analysis, data verification was performed.

2.4 Data analysis

For manufacturers working along the principles of a continuous cycle of improvement, medical device modification and risk analysis update were expected to be coupled because device modification should always be incorporated in the risk analysis. This coupling was demonstrated by coinciding device modification and risk analysis update, i.e. manufacturers replied positively to device modification as well as risk analysis update. However, a risk analysis update does not necessarily lead to a device modification.
A comparison was made between current and previous versions of procedures to determine the effect of periodic revision on the content of procedures. For the product category concerning medical devices intended for clinical investigation, the comparison focussed on PMS as well as vigilance procedures. For infusion pumps, the comparison was limited to the PMS procedure as vigilance procedures were not requested for the previous investigation. For endoscope washer disinfectors, a comparison was not possible because procedures were not submitted previously.
Procedure revision should keep the essential procedure items, if present, or should incorporate items if absent previously. However, there is also a possibility that procedure revision omitted items in the current procedure version. Only if the item was not covered in another procedure, this omission was considered a shortcoming. If an item remained absent in both versions and the item was not covered in another procedure, this absence was also considered a shortcoming.

3 Results

3.1 Submission of questionnaire and procedures

Questionnaires and procedures were received from February 2008 to April 2008. The majority of manufacturers (71 %; 25/35) needed a reminder for questionnaire and/or procedures submission. In general, questionnaires were more readily submitted than procedures.

Medical devices intended for clinical investigation
Almost every manufacturers (89 %; 16/18) submitted questionnaires (Figure A1A, Appendix III). Two manufacturers did not submit questionnaires (and procedures), because one manufacturer went out of business, and the second one did not place devices on the European market and had no EU-authorised representative (Table A1, Appendix IV). Both manufacturers were excluded from this investigation. PMS and vigilance procedures were submitted by eleven and thirteen manufacturers, respectively. Internet searches revealed that manufacturers, who did not submit procedures, had no other CE-marked medical devices (yet) with the exception of one manufacturer. This manufacturer did not respond upon reminding. In general, the timeliness of submissions was adequate, i.e. before the submission deadline.

Infusions pumps
Almost every manufacturer (91 %; 10/11) submitted questionnaires and procedures (Figure A1B, Appendix III; Table A2, Appendix IV). One manufacturer submitted nothing despite several reminders. In general, the timeliness of manufacturers' submissions was adequate.

Endoscope washer disinfectors
All six manufacturers submitted questionnaires and procedures (Figure A1C, Appendix III; Table A2, Appendix IV). However, the timeliness of manufacturers' submissions could be improved.

3.2 Regulatory approval of medical devices for clinical investigation

Between the time of notification to the Health Care Inspectorate concerning the start of the clinical investigation (date of notification ranged from April 2005 – March 2006) and the mailing of questionnaire (February 2008), several medical devices obtained regulatory approval and were released on the market (n=8). One medical device was CE-marked, but market release was postponed. Other medical devices were not (yet) CE-marked (n=8), or were withdrawn after market release (n=2). For an overview see Table A1, Appendix IV.

3.3 Device modification-risk analysis interaction

For manufacturers working along the principles of a continuous cycle of improvement, medical device modification and risk analysis update were expected to be coupled. This coupled interaction is shown in Figure 2A-C for our sample of medical devices.
Overall, 48 % of the medical devices (16/33) were modified with concurrent risk analysis update, suggesting the desired coupled interaction. 21 % of the devices (7/33) were not modified and the related risk analyses not updated. 9 % of the risk analyses (3/33) were updated without device

modification (ascending lines in Figure 2B-C). For both these groups, no conclusion can be drawn on the presence of a coupled interaction. 18 % of the medical devices (6/33) were modified without an update of the risk analysis (descending lines in Figure 2A-C), showing no coupled interaction. It is remarkable that these manufacturers did not consider the device modifications worth mentioning in the risk analysis, while the nature of these modifications were related to changes in design, materials, system components, manufacturing, label, instructions for use, and software (Table A4 and A6, Appendix IV).
Reasons given for risk analysis update were data obtained from observations during clinical investigation, and post-market experiences obtained from PMS and vigilance activities (53 %; 10/19) (Table A3 and A5, Appendix IV). Often other reasons were given such as new design and changes in manufacturing process (42 %; 8/19). For one medical device, no reason was given. Reasons given for risk analysis update for devices without modification were 'adjustment to an internal standard operating procedure', 'periodic review/update to check whether there were new findings not included in the risk analysis so far', and 'updated in the light of ongoing clinical experience'.

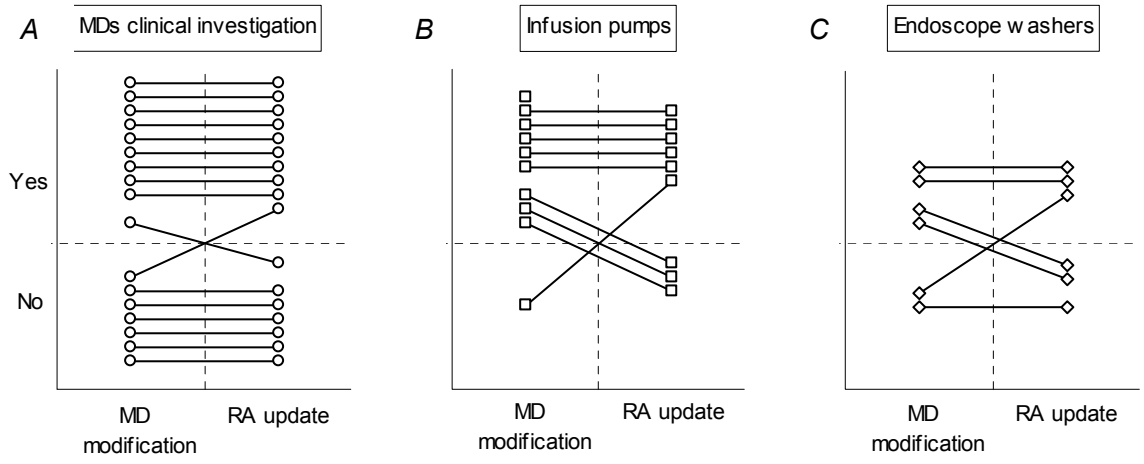

Figure 2. Interaction between device modification and risk analysis. Relationships concerning modification of medical device (MD) and update of risk analysis (RA) are shown for medical devices intended for clinical investigation (A), infusion pumps (B), and endoscope washer disinfectors (C).

Medical devices intended for clinical investigation
Since the start of the clinical investigation, ten of seventeen medical devices were modified but for only nine medical devices the related risk analyses were updated (Figure 2A). Seven medical devices were not modified, but for one medical device the related risk analysis was updated. The nature of device modifications was mainly related to changes in design (73 %; 8/11), label (36 %; 4/11), and instructions for use (36 %; 4/11) (Figure A2, Appendix III; Table A4, Appendix IV). Manufacturers could indicate more than one type of modification per medical device.

Infusions pumps
Nine of ten infusion pumps were modified but only five related risk analyses were updated (Figure 2B). For one infusion pump, the manufacturer stated that 'the risk analysis, hazard analysis, FTA & FMEA […] was effective on February 2006'. FTA is Fault Tree Analysis and FMEA is Failure Modes and Effects Analysis. This was interpreted as an unclear risk analysis update, i.e. neither 'yes' nor 'no' was

assigned. For a second infusion pump, the risk analysis was updated but without device modification. The nature of modifications was mainly related to design changes (78 %; 7/9), instructions for (67 %; 6/9), label (44 %; 4/9), and materials (44 %; 4/9) (Figure A2 Appendix III; Table A6, Appendix IV).

Endoscope washer disinfectors
Four of six endoscope washer disinfectors were modified but only two related risk analyses were updated (Figure 2C). Two endoscope washer disinfectors were not modified, including one device with a risk analysis update. The nature of modifications was mainly related to changes in design (75 %; 3/4), systems components (75 %; 3/4), materials (50 %; 2/4), and software (50 %; 2/4) (Figure A2, Appendix III; Table A6, Appendix IV).

3.4 Relationship between device experience and modification

3.4.1 Finding leading to device modification

Relationships between pre-market and post-market device experiences and modifications of medical devices are shown in Figure 3. The relationships represent the answers to questions 5-6-7 of the questionnaire for medical devices clinical investigation, and questions 3-4 for infusion pumps and endoscope washer disinfectors. The data should be interpreted as a relationship between one event (cause, i.e. experience-based finding) resulting in another event (effect, i.e. device modification). Overall, findings based on device experiences gathered from clinical investigations and PMS activities often led to modification of medical devices (50 % and 55 %, respectively; 8/16 and 12/22, respectively), whereas vigilance activities resulted less often in device modifications (25 %; 5/20).

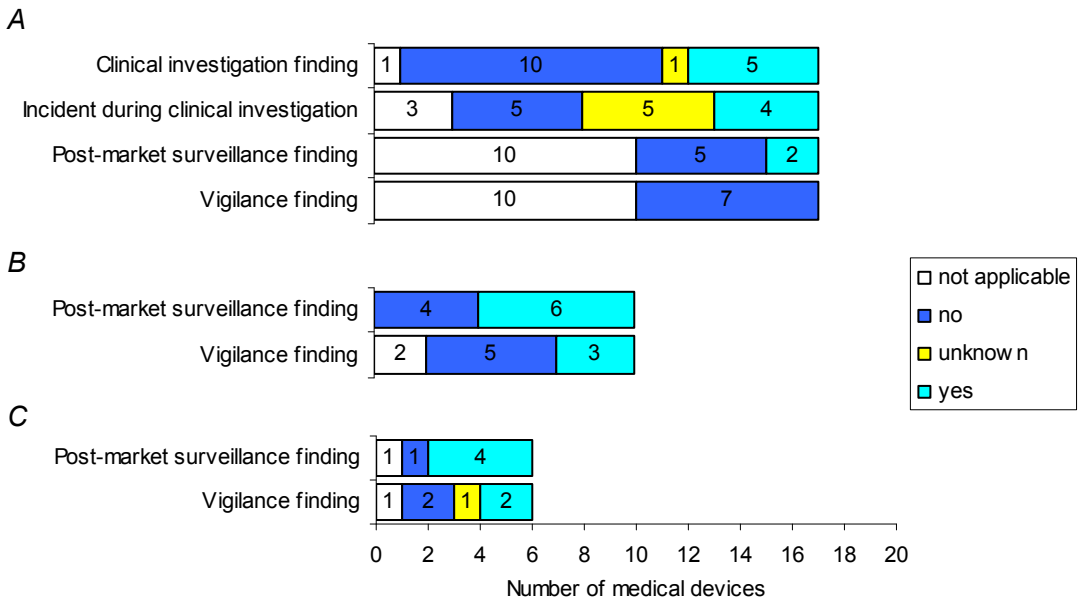

Figure 3. Experience-based modifications to medical devices. Pre-market and post-market findings used for device modification concerning medical devices intended for clinical investigation (A), infusion pumps (B), and endoscope washer disinfectors (C).

Medical devices intended for clinical investigation
Modifications of medical devices previously under investigation were based upon findings gained from clinical investigations (31 %; 5/16) as well as incidents during clinical investigations (29 %; 4/14) (Figure 3A). Modifications of medical devices, which subsequently were released on the market, were based on findings from PMS activities (29 %; 2/7) but never on findings from vigilance activities.

Infusions pumps
Modifications of infusion pumps were mainly based upon findings from PMS activities (60 %; 6/10) and less on vigilance activities (38 %; 3/8) (Figure 3B). For infusion pumps without vigilance-based device modification, two manufacturers gave additional training or made a training poster available to remind users and sales teams continuously about the way the infusion pumps should be used.

Endoscope washer disinfectors
Modifications of endoscope washer disinfectors were mainly based upon findings from PMS activities (80 %; 4/5) and less on vigilance activities (40 %; 2/5) (Figure 3C).

3.4.2 Device modification as consequence of finding

Relationships between medical device modifications and pre-market and post-market device experiences are shown in Figure 4 A-C (upper bars). The relationships represent the answers to question 3 of the questionnaire for medical devices clinical investigation, and question 1 for infusion pumps and endoscope washer disinfectors. The data should be interpreted as an event (effect, i.e. device modification) caused by another event (cause, i.e. experience-based finding). The reversed order (i.e., finding leading to modification, see Figure 3) is also shown in Figure 4A-C (lower bars). It was expected that the answers for the events leading to modifications and the events underlying modifications should be comparable. Figure 4 shows that the answers to the same topic differ. For the device used in clinical investigations and the infusion pumps, experience-based findings were less often mentioned. For the endoscope washer-disinfectors, no findings were mentioned.

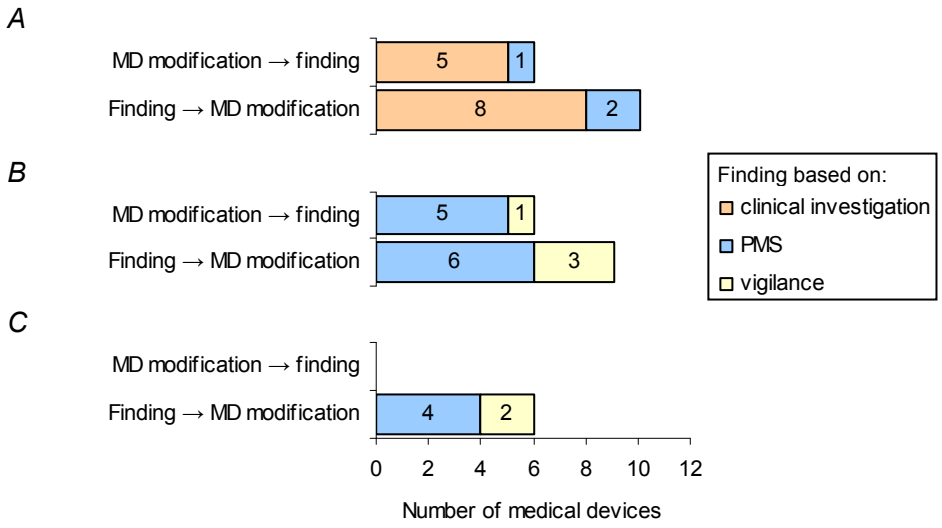

Figure 4. Reasons for medical device modification (MD) and findings from pre-market device experiences (clinical investigation) and post-market experiences (PMS and vigilance) leading to device modification for the product categories concerning medical devices intended for clinical investigation (A), infusion pumps (B), and endoscope washer disinfectors (C).

3.5 PMS procedures

3.5.1 Content of current procedures

A PMS procedure should contain both active and passive elements. Active and passive customer feedback were described in 63 % and 89 % of the submitted procedures, respectively (Figure 5A-B; upper-right quadrant). Post-market clinical follow-up was mentioned in 29 % of the procedures (Figure 5C). In none of the procedures, the guideline relating to medical devices directives (so-called MEDDEV guideline) 2.12-2 (May 2004) on post-market clinical follow-up was mentioned (data not shown). In 52 % of the procedures, review of (scientific) literature was mentioned as means of gathering information on medical device experiences (Figure 5D). Risk management activities were mentioned in 41 % of the procedures (Figure 5E). It is conceivable that manufacturers did actually elaborate on these activities in other procedures, for instance in a procedure for corrective and preventive action (CAPA). Such procedures were not requested, but in 63 % of the PMS procedures a CAPA procedure was referred to (Figure 5F). In combination, 78 % of the manufacturers mentioned or referred to risk management activities and/or a CAPA procedure in the PMS procedure (Figure A3, Appendix III). Thus, it cannot be excluded that more manufacturers performed risk management activities due to findings of PMS activities. 81 % of the procedures were dated and the average date of issue was January 2007. The average period between the current and a previous PMS procedure version was 35±23 months (Table A7, A8 and A11, Appendix IV).
In conclusion, PMS procedures lacked the description of a systematic approach for pro-active gathering of device experiences, and the use of PMS findings as input for a review of the current risk analysis and for CAPA by means of systematic procedure reference.

3.5.2 Revision of procedures

For twelve of the submitted PMS procedures, a previous version was available from earlier studies. For these twelve pairs of procedures, the effect of procedure revision on essential procedure items was determined (Figure 5 represented by lines connecting markers). Revision led to nine newly incorporated items (ascending lines in Figure 5A, 5C-F). For most procedures, items remained in the procedures if present initially (upper horizontal lines) (Table A7-A8, Appendix IV). For four items, however, revision led to omission upon revision, without referring to other procedures covering these omitted items (descending lines in Figure 5B-E). This concerned two procedures. The most unfavourable outcome was in case items remained unmentioned without referring to other procedures covering missing items. This applied to all lower horizontal lines, except for the one in Figure 5B. In this particular pair of PMS procedures, complaints were excluded explicitly, and the manufacturer referred to a complaint procedure, which described a passive approach for information gathering. Because of the reference of a separate procedure, this was not considered a shortcoming.
Overall, the percentage of essential procedure items present in previous and current PMS procedures was 54 % (39/72) and 61 % (44/72), respectively. Thus, the quality of current procedures was slightly better compared with previous versions. Definitely, current PMS procedures left room for improvement.

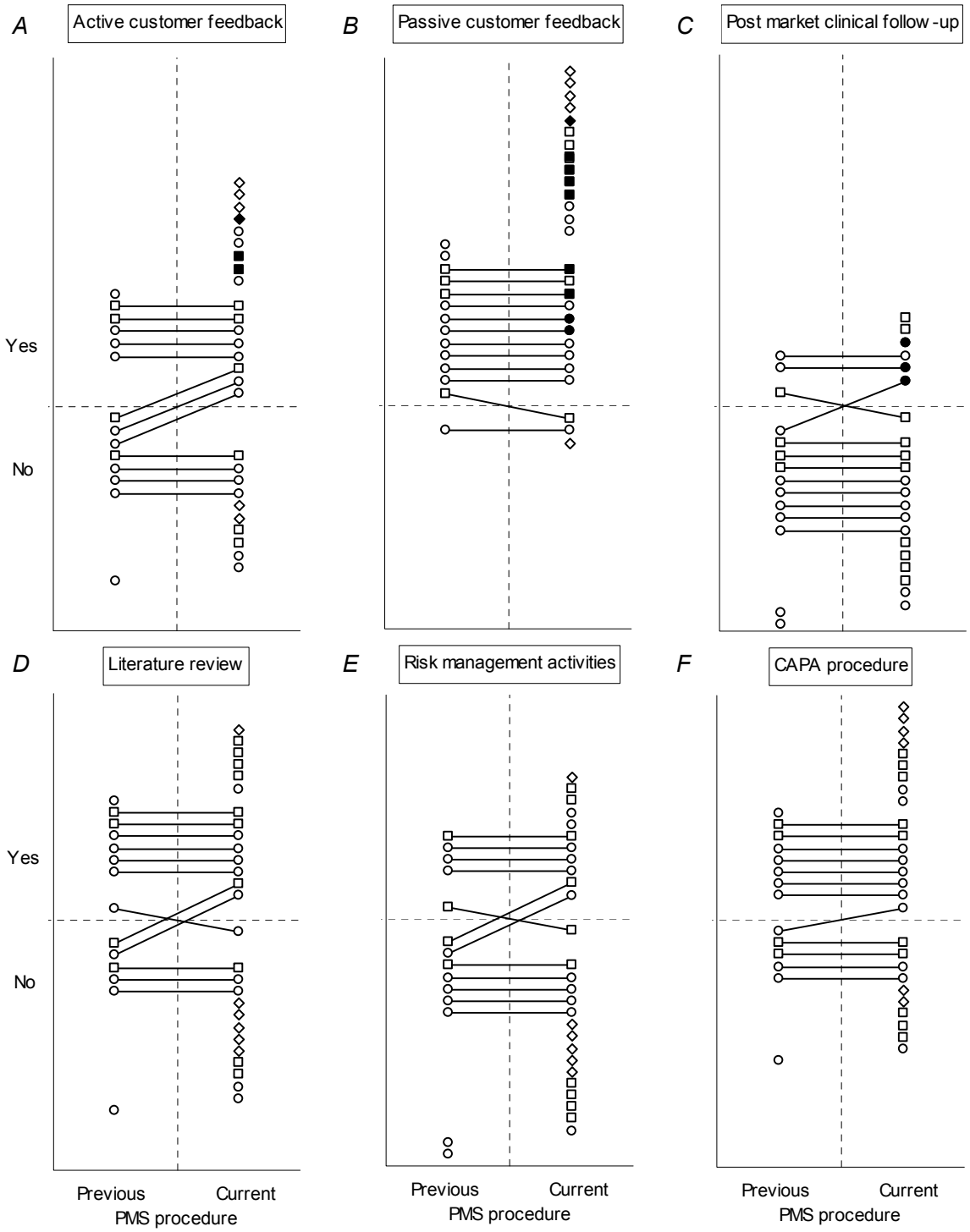

Figure 5. Presence of items in current and previous PMS procedures. Markers represent essential procedures items for medical devices intended for clinical investigation (dots), infusion pumps (squares), and endoscope washer disinfectors (diamonds). Solid markers indicate implemented PMS activities (A-D) which were laid down as written rules in the procedure. For endoscope washer disinfectors, post-market clinical follow-up was considered not relevant.

3.6 Vigilance procedures

3.6.1 Content of current procedures

All vigilance procedures described a systematic approach for incident monitoring and evaluation, and the legal and time-limited obligation for manufacturers to convey information about incidents to competent authorities, i.e. notification obligation (Table A9-A10, Appendix IV). However, the use of vigilance findings as input for risk re-assessment and CAPA was often not described. Risk management activities were mentioned in 28 % of the procedures (Figure 6A; upper-right quadrant). It is conceivable that manufacturers did actually elaborate on these activities in other procedures, for instance in a CAPA procedure. In 41 % of the vigilance procedures, a CAPA procedure was referred to (Figure 6B). In combination, 52 % of the manufacturers mentioned risk management activities and/or a CAPA procedure in the vigilance procedure (Figure A3A-C, Appendix III). Thus, it cannot be excluded that more manufacturers performed risk management activities due to findings of vigilance activities. In 79 % of the vigilance procedures (the principle of) field safety corrective action (FSCA, also referred to as recall) was mentioned (Figure 6C). In 45 % of the vigilance procedures, a correct reference of the MEDDEV Guidelines on vigilance reporting was incorporated, i.e. the appropriate MEDDEV version matched the date of issue of the vigilance procedure. None of the procedures dated January 2008 or later referred to the current MEDDEV guidance document. Two procedures mentioned the MEDDEV Guidelines on post-market clinical follow-up (data not shown). On average, the date of issue was December 2006. The period between the current and a previous vigilance procedure version was 33±14 months (Table A9-A11, Appendix IV).
In conclusion, vigilance procedures fully addressed incident reporting and the obligation to notify competent authorities. However, procedures did not describe using vigilance findings as input for a review of the current risk analysis and for CAPA by means of systematic procedure reference. Moreover, manufacturers need to bring their vigilance procedure in line with the current MEDDEV.

3.6.2 Revision of procedures

For ten of the submitted vigilance procedures, a previous version was available from an earlier study. For these ten pairs of procedures, the effect of procedure revision on the presence of essential vigilance items was determined (Figure 6, represented by lines connecting markers). In all previous and current vigilance procedures, incident reporting and notification obligation to competent authorities were fully addressed (Table A7, Appendix IV). Revision led to four newly incorporated items (ascending lines in Figure 6B-C). For the majority of items, revision kept items if present. For two items, however, revision led to omission without referring to other procedures covering these omitted items (descending lines in Figure 6A-B). The most unfavourable outcome was in case items remained unmentioned without referring to other procedures covering missing items (lower horizontal lines in Figure 6A-C). Overall, the percentage of essential procedure items present in previous and current vigilance procedures was 62 % (31/50) and 66 % (33/50), respectively. Thus, the quality of current procedures only improved slightly upon revision. Definitely, current vigilance procedures left room for improvement.

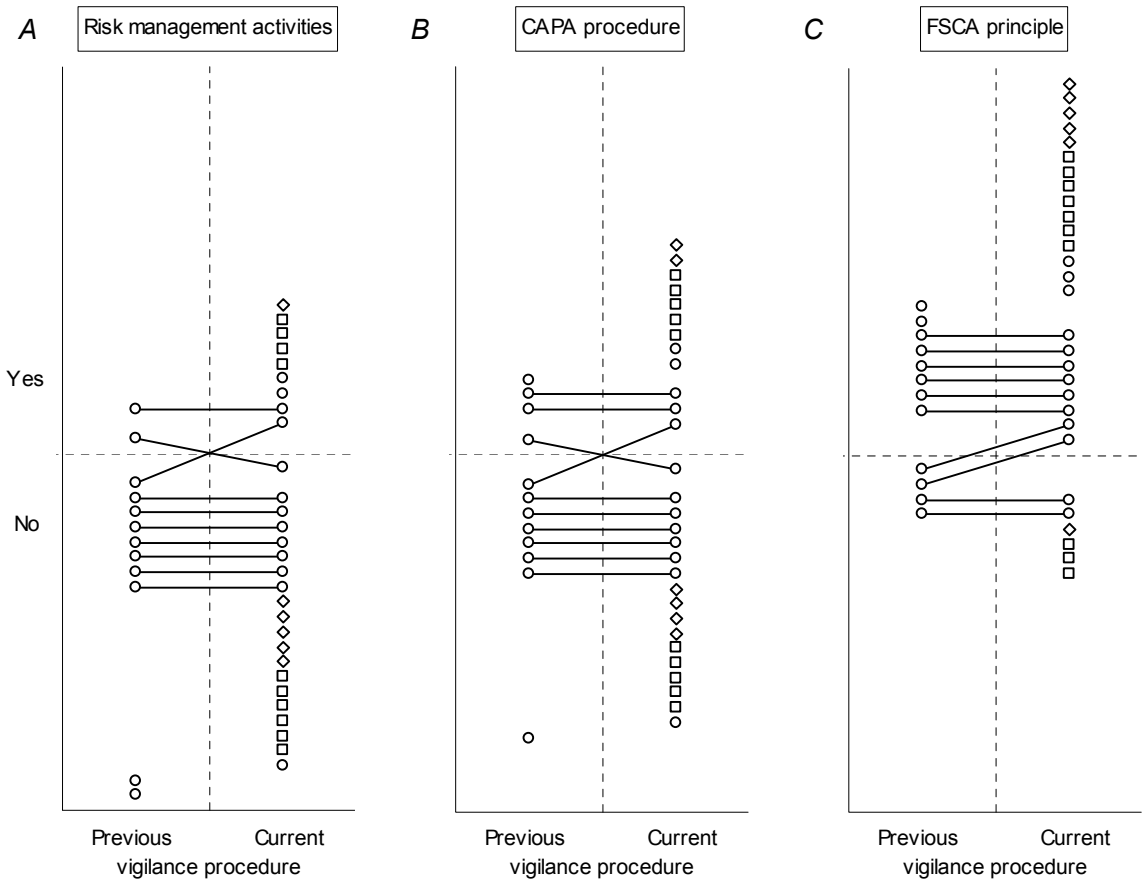

Figure 6. Presence of items in current and previous vigilance procedures. Markers represent essential procedure items, i.e. risk management activities (A), CAPA procedure (B), and FSCA principle (C), for medical devices intended for clinical investigation (dots), infusion pumps (squares), and endoscope washer disinfectors (diamonds). Note that previous vigilance procedures were only obtained for medical devices intended for clinical investigation. In addition, incident reporting and notification obligation to competent authorities are not shown, because both essential items were fully addressed in previous as well as current vigilance procedure.

4 Discussion

We used a questionnaire to examine whether manufacturers use device experiences for quality improvement of medical devices. The questionnaire indicated whether device modification and update of the risk analysis coincided. Additionally, the questionnaire revealed whether manufacturers managed to use findings from clinical investigations and after sales activities (including PMS and vigilance) as input for the modification of medical devices. Moreover, the content of PMS and vigilance procedures encompassing crucial items were checked upon. A comparison between previous and current procedures highlighted whether procedure revision resulted in improvement of procedures. Risk management activities, post-market surveillance and vigilance procedures are vital cornerstones of a continuous cycle of medical device improvement.
Previous investigations indicated that the implementation of a continuous cycle of improvement left room for improvement [5, 6]. Shortcomings of procedures were related to the absence of a description of risk management activities and CAPA activities. A system to collect and review information on medical devices in the post-production phase is an essential part of risk management [2] and even an explicit regulatory requirement [1]. However, we are not aware of previously published investigations on the presence and implementation of such systems. In a sample of manufacturers developing and marketing three categories of medical devices, our results provide some evidence as to the level of implementation of a continuous cycle of improvement. We feel that manufacturers, notified bodies and competent authorities could learn valuable lessons from these results when setting up, respectively auditing quality management systems. Considerations in the following sections of the discussion will focus on manufacturers.

Device modification – risk analysis update interaction
One of our main findings was that for a substantial number of manufacturers (22 %; 7/32), two crucial elements of the continuous cycle of improvement did not coincide, i.e. medical device modification and risk analysis update were not coupled. For several other manufacturers (31 %; 10/32), no definite conclusion could be drawn with regard to the presence of this coupling. This means coupling is present in at least 47 % of the manufacturers (15/32) in our sample, but could eventually increase up to 78 % (25/32). A device modification can be the result of an update of the risk analysis, in which case the coupling is obvious. Risk analysis updates do, however, not necessarily lead to a device modification. Vice versa, a device modification should always lead to an update of the risk analysis as any change in a device could introduce new risks or modify the estimate of previously identified risks. Therefore, it calls for an update of the risk analysis.

Device modification – experiences
Manufacturers were asked whether an experience-based finding had led to device modification. Findings based on device experiences from clinical investigations and PMS activities often led to modification of medical devices (50 % and 55 %, respectively), which suggests that these outcomes are seriously considered and provide leads for device modification. On the other hand, vigilance activities resulted less often in device modifications (25 %). This suggests that adverse events leading to a vigilance report are often judged not to be directly related to the design or the instructions for use of the device itself.
Manufacturers were also asked what reason underlay a device modification. This is the opposite from the questions above. Although it was expected that the answers would give similar results, the number of positive answers was considerably lower. This discrepancy is most likely caused by the fact that open-ended questions were used in the questionnaire and that both lines of questions did not

immediately follow each other. Moreover, a modification of the instructions for use may not have been considered as a modification of the device by the respondents. In the questionnaire it was explicitly stated in the first line of questioning that design as well as labelling modification should be regarded as a modification of the device. This statement was, however, not repeated at the second series of questions.

Active and passive PMS procedures
A crucial aspect of PMS is gathering of medical device experiences by means of a systematic proactive approach, including active customer feedback, post-market clinical follow-up (where applicable), and literature reviews. The importance of a proactive approach for collecting device experiences is to observe trends which can help manufacturers to improve user/patient satisfaction, and to identify opportunities for medical device improvement contributing to the continuous process ensuring the safety of (the use of) medical devices.
The present investigation revealed that manufacturers described in their PMS procedures more passive feedback (89 %) than active feedback (63 %). In a previous investigation, similar results were found for manufacturers following the conformity assessment procedure described in Annex II of the MDD [5]. An ideal procedure should address both active and passive elements to gain feedback yielding a 100 % score for both methods. In our current investigation, manufacturers were requested to submit PMS procedures and not complaint procedures. PMS procedures scored positively (i.e., 'yes') on passive customer feedback only if the collection and review of complaints was actually described. Merely referring to a complaint procedure in the PMS procedure yielded a negative score (i.e., 'no'). Two out of three current PMS procedures without describing passive customer feedback (Figure 5B) referred to a complaint procedure which was not submitted. If such a reference had been scored positively, the percentage of passive customer feedback would have been 96 %.
Although we did not request explicitly which finding was based on a particular PMS activity, several manufacturers provided some insight in the way they implemented procedural rules. Remarkably, review of (scientific) literature was never included as PMS activity-based finding in responses. The impression is put forward that the actual implementation of various PMS activities might lag behind written rules in the procedure. This might suggest a gap between procedural requirements and 'daily' practice. However, if we had explicitly asked for it in our questionnaire, we might have elucidated the apparent discrepancy.

Post-market clinical follow-up
It is remarkable that post-market clinical follow-up was less of an issue for manufacturers involved in research and development of long-term implantable medical devices which were included in the product category concerning medical devices intended for clinical investigation. In particular for manufacturers of endovascular implants, post-market clinical follow-up is needed because it can provide invaluable 'real-world' data to establish long-term safety and performance of medical devices. For instance, off-label use of coronary drug-eluting stents is very common in percutaneous coronary intervention [12-14] and off-label use is considered a strong indicator for conducting post-market clinical follow-up studies. For devices like coronary stents, post-market clinical follow-up should be part of the clinical evaluation. In the amended MDD [1], clinical evaluation is part of essential requirement 6a. Furthermore, it is required that the clinical evaluation and its documentation is actively updated with data obtained from the post-market surveillance.

Risk management activities and CAPA
PMS and vigilances procedures had two shortcomings in common. First, the lack of using PMS findings as input for an update of the risk analysis. It cannot be excluded, however, that more manufacturers performed risk management activities due to PMS findings. It is conceivable that manufacturers, who did not refer to risk management activities in surveillance procedures, actually did

elaborate on these activities in their CAPA and/or risk management procedures. Sound quality and risk management systems should integrate risk management activities in market surveillance and CAPA procedures. Second shortcoming, however, is the absence of a reference in the PMS and vigilance procedures to a CAPA procedure and/or a risk management procedure in which it is described how surveillance findings can lead to the decision to initiate CAPA and eventually risk re-assessment. Although almost every manufacturer used the abbreviation CAPA in its procedures (data not shown), only half of the manufacturers referred to a procedure. In our opinion, a procedure reference is a good indicator for the presence of a CAPA system which is an organizational structure with defined responsibilities, processes, procedures, and resources for implementing quality and risk management. It could be argued that risk management activities and CAPA are not within the scope of a vigilance procedure. Strictly speaking, a vigilance procedure could be solely focused on gathering information on incidents and reporting incidents to competent authorities. However, vigilance is part of the MDD requirement to have a systematic procedure to review device experience and apply corrective action if necessary [1]. Therefore, we consider risk management activities and CAPA as essential items of a vigilance procedure. If these items are not described in the vigilance procedure, at least a reference to relevant standard operating procedures should be included.

MEDDEV Guidelines

MEDDEV documents reflect the positions taken by different stakeholders in the medical device sector, i.e. competent authorities, European Commission, notified bodies, industry and other interested parties. Although the MEDDEV documents are not legally binding, it is anticipated that the guidelines will be followed and expected that manufacturers and their EU-authorised representatives comply.
It is remarkable that manufacturers did not widely adopt the MEDDEV Guidelines on post-market clinical follow-up published in 2004 [3]. This document provides guidance to identify and investigate long-term performance and safety issue which become apparent only after widespread use. The MEDDEV Guidelines on post-market clinical follow-up were never referred to in PMS procedures. Instead, two vigilance procedures (7 %) mentioned the guidelines. However, manufacturers did not elaborate on it further, indicating that they adapted their practice as needed. Apparently, the concept requires further clarification to be consistently and unanimously understood and implemented by manufacturers. The new EU Working Group on Clinical Investigation and Evaluation (former Clinical Evaluation Task Force) and the Global Harmonization Task Force (Study Group 5 – Clinical Safety/Performance) are planning to propose updated/new guidelines [personal communication].
In contrast, the MEDDEV Guidelines for vigilance reporting [4, 15] were well-adopted, i.e. 83 % of the vigilance procedures referred to these guidelines. However, manufacturers did not always apply the current version or omitted revision number and year of publication. Approximately half of the vigilance procedures were dated July 2007 or later, but only one fourth of these procedures actually referred to the current version of the MEDDEV Guidelines on vigilance reporting, i.e. revision 5 of April 2007 [4]. None of the vigilance procedures dated January 2008 or later referred to the current version. This MEDDEV document was published on the European Commission website in June 2007 and the guidelines became effective January 1, 2008. Thus, manufacturers need to bring their procedures in line with current MEDDEV Guidelines.

Revision of procedures

At the time of our request for procedure submission, a substantial part of manufacturers had not revised their procedures for a considerable period of time, i.e. on average not within two years. This suggests that the process of procedure management tends to be a rather static system. At least a two-year revision should be implemented enabling dynamic evolution and continuous improvement of procedures. Currently, this is especially important because of recent regulatory changes and revisions of MEDDEV documents. In general, procedure revision hardly affected the content of PMS and vigilance procedures. Thus, these surveillance procedures leave room for further improvement, which

could be implemented during the next procedure revision. In our opinion, the improvement of the content of the procedures is an item that notified bodies should address when auditing the quality management systems of manufacturers of medical devices.

Limitations of the investigation

Our investigation has several limitations. First, we used a questionnaire with open-ended questions. Manufacturers were free to choose the level of detail in their answers. Therefore, data extraction from answers was crucial, but also limited by the available information. In particular, the chain of events regarding surveillance activity-finding-device modification was sometimes difficult to establish. Especially, answers to questions concerning findings not leading device modification did not give adequate information. Apparently, the distinction made between findings leading to modification and findings not leading to modification was not clear to manufacturers. However, we believe that open-ended questions will trigger manufacturer to less socially-desirable responding. Social desirability bias is usually found in research carried out in the form of questionnaires. A second limitation is that we did not ask explicitly for PMS and vigilance findings or device modifications which were actually related to updates of the risk analysis, thus strictly speaking not proving causality. We only asked for both elements separately, again to avoid social desirable responses. This means we might have overestimated the implementation of the continuous cycle of improvement. A third limitation of our investigation is the relatively small number of manufacturers. In addition, our medical device stratification was restricted to three specific product types from medical devices risk Classes IIa, IIb, and III. Whether our findings are similar for Class I medical devices remains to be elucidated and generalizations of our results to other types of medical devices should be performed carefully. A fourth limitation is that we had no information on the professional affiliation of the person who filled in the questionnaire. It is possible that current answers represent the response of a heterogeneous sample of professionals with varying oversight of all elements of a manufacturer's continuous cycle of improvement. Despite these limitations, our investigation provides some evidence that at least half of the manufacturers implemented the continuous cycle of improvement for medical devices, while this concept is still in its infancy for a substantial part of manufacturers, especially the fact that it requires not only operationally sound procedures but also their correct implementation.

Implications for patient safety

The main goal of the regulatory requirements related to a continuous cycle of improvement of medical devices is to ensure the safety of patients, users or other persons. Obviously, this is of primary importance to all involved stakeholders. Especially for manufacturers, an additional incentive to implement a continuous cycle of improvement might be the commercial advantages of an ongoing improvement of user and patient satisfaction.

Although the identified shortcomings in the implementation of the continuous cycle of improvement do not necessarily mean that the quality and safety of the actual medical devices are also inadequate, there is certainly a reason for concern. Failure to implement the continuous cycle of improvement means there are risks for avoidable incidents, both for current and future products. We call upon all involved stakeholders to work together and aim at a well functioning continuous cycle of improvement.

5 Conclusion

- Many manufacturers implemented the continuous cycle of improvement of medical devices, but for a substantial part of manufacturers this concept is still in its infancy. Major issues are the following:
  - A crucial element of the continuous cycle of improvement was not coupled, i.e. medical device modification and risk analysis update were not tuned.
  - The procedural implementation of post-market clinical follow-up is not yet established.
  - Risk management activities and CAPA are underexposed in PMS and vigilance procedures.
  - Experiences gathered from clinical investigations and PMS activities more often lead to device modification than vigilance activities.
  - The quality of PMS and vigilance procedures still leaves room for further improvement. Revision of procedures has a marginal effect on the content of procedures.
  - Manufacturers need to bring their vigilance procedure in line with the current MEDDEV guideline.
- Further implementation of the continuous cycle of improvement of medical devices is necessary to optimise the safety of patients, users and other persons.

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Appendix I Questionnaires

Questionnaire for the product category including medical devices intended for clinical investigation:

1. Is the medical device currently CE-marked and released to the market?
   - ☐ Yes
   - ☐ No

   If yes, please give date of CE-mark approval and market release
   - CE-mark approval date (DD-MM-YYYY):
   - Market release date:

   If not, please mark the following (multiple answers are possible):
   - ☐ Clinical investigation stopped early, please give reason why and go to Q 3 to 5;
   - ☐ Clinical investigation is suspended, please give reason why and go to Q 3 to 5;
   - ☐ Clinical investigation is still ongoing, go to Q 3 to 5;
   - ☐ CE-mark approval is pending with the notified body,
     - please indicate expected date of approval and market release and go to Q 3 to 5;
     - Expected CE-mark approval date (DD-MM-YYYY):
     - Expected market release date:
   - ☐ Medical device will not be marketed, please give reason why not;
   - ☐ Other reason, please give short description

2. Has the name of medical device been changed?
   - ☐ Yes, new (brand) name:
   - ☐ No

3. Has the medical device been modified (i.e., design, label, and instructions for use) since the start of the clinical investigation?
   - ☐ Yes, identify the nature of and the reason for these modifications
   - ☐ No

4. Has the risk analysis of the medical device been updated since the start of the clinical investigation?
   - ☐ Yes, identify the nature of and the reason for these modifications
   - ☐ No

5a. What are the findings of the clinical investigation?
5b. Were there any incidents during the clinical investigation?
5c. Which findings/incidents have led to which modification(s) of the device?
5d. Which findings/incidents did not lead to a modification of the medical device and why not?

6a. What are the findings of the post-market surveillance activities since market release?
6b. Which findings have led to which modification(s) of the medical device?
6c. Which findings did not lead to a modification of the medical device and why not?

7a. What are the findings of the vigilance activities since market release?
7b. Which findings have led to which modification(s) of the medical device?
7c. Which findings did not lead to a modification of the medical device and why not?

8. Please submit a copy of your current post-market surveillance procedure.

9. Please submit a copy of your current vigilance procedure.

Questionnaire for product categories including infusion pumps and endoscope washer disinfectors:

1. Has the medical device been modified (i.e., design, label, and instructions for use) since two years?
   ☐ Yes, identify the nature of and the reason for these modifications
   ☐ No

2. Has the risk analysis of the medical device been updated since two years?
   ☐ Yes, identify the nature of and the reason for these modifications
   ☐ No

3a. What are the findings of the post-market surveillance activities since two years?
3b. Which findings have led to which modification(s) of the medical device?
3c. Which findings did not lead to a modification of the medical device and why not?

4a. What are the findings of the vigilance activities since market release?
4b. Which findings have led to which modification(s) of the medical device?
4c. Which findings did not lead to a modification of the medical device and why not?

5. Please submit a copy of your current post-market surveillance procedure.

6. Please submit a copy of your current vigilance procedure.

Appendix II Data extraction from procedures

PMS procedure
Data extraction from PMS procedures included the following items:

- A description of the systematic process for collecting and reviewing information on device experiences. Although many potential sources can be used, procedures should mention the following important activities:
  - active customer feedback, e.g. customer survey of end-users or distributors;
  - passive customer feedback, e.g. customer / product complaints;
  - post-market clinical follow-up, e.g. extended follow-up of patients (or a subset of patients) enrolled in pre-market clinical investigation, prospective studies of a representative subset of patients, open registries;
  - literature review, e.g. review of scientific publications.
- A description of risk management activities. The findings of the surveillance activities should be used as input to risk re-assessment starting with performing risk analysis and contributing through the subsequent steps of the medical device risk management process. Procedures were checked upon whether an update of the risk analysis was mentioned;
- Corrective and preventive action (CAPA). A corrective action is taken to prevent the recurrence of a potential non-conformity or other undesirable situation. Preventive action is taken to prevent occurrence. Procedures were checked upon whether:
  - a CAPA procedure reference (i.e., title and document number) was mentioned;
  - findings of PMS activities led to the initiation of CAPA. It is conceivable that a CAPA can also be opened indirectly based on a change in severity and occurrence of product failure from the risk assessment.
- Reference to the European guidance document on post-market clinical follow-up. In case the PMS procedure was dated July 2004 or later, the procedure should comply with the MEDDEV Guidelines on post-market clinical follow-up [3].

Vigilance procedure
Data extraction from vigilance procedures included the following items:

- a description of the systematic process for collecting and reviewing information on device safety, i.e. incident reporting;
- a description of the notification obligation for manufacturers concerning reporting of incidents to competent authorities;
- a description of risk management activities (see risk management activities in PMS procedure);
- CAPA (see CAPA in PMS procedure);
- reference to guidance documents on vigilance requirements for medical devices. In case the vigilance procedure was dated July 2007 or later, the procedure should comply with the current MEDDEV Guidelines on a medical devices vigilance system [4]. Procedures dated between July 2001 and July 2007 should comply with the preceding version of the MEDDEV Guidelines on vigilance, published in April 2001 [4];
- field safety corrective action (FSCA), i.e. the term FSCA should be mentioned in the vigilance procedure. Although the term FSCA has been introduced in the current MEDDEV Guidelines on vigilance [4], the principle of FSCA was already described in the previous version of the MEDDEV Guidelines and was termed recall. A FSCA is an action taken by the manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of

a medical device. A FSCA should be notified via a field safety notice, which is a communication to customers and / or users sent out by the manufacturer.

Identification of procedures
For the identification of procedures the following information was used:

- author of the procedure or responsible business unit if author was not indicated;
- date of issue or version number if date was not indicated.

In case of identical procedures (see below), data extraction was limited to the currently submitted procedure.

Revision of procedures
The effect of periodic revision on PMS and vigilance procedures was determined by comparing the content of previous and current versions of procedures. For content of procedures we focused on items in the sections mentioned above. In case it was impossible to distinguish between an earlier and more recent version of the procedure, procedures were considered identical and they were not compared. Distinct procedures were identified if:

- date of issue differed;
- version number of procedures differed for procedures without date of issue;
- content of procedures differed for procedures without date of issue and version number. In such case, the content of procedures was checked page-by-page.

Appendix III Figures

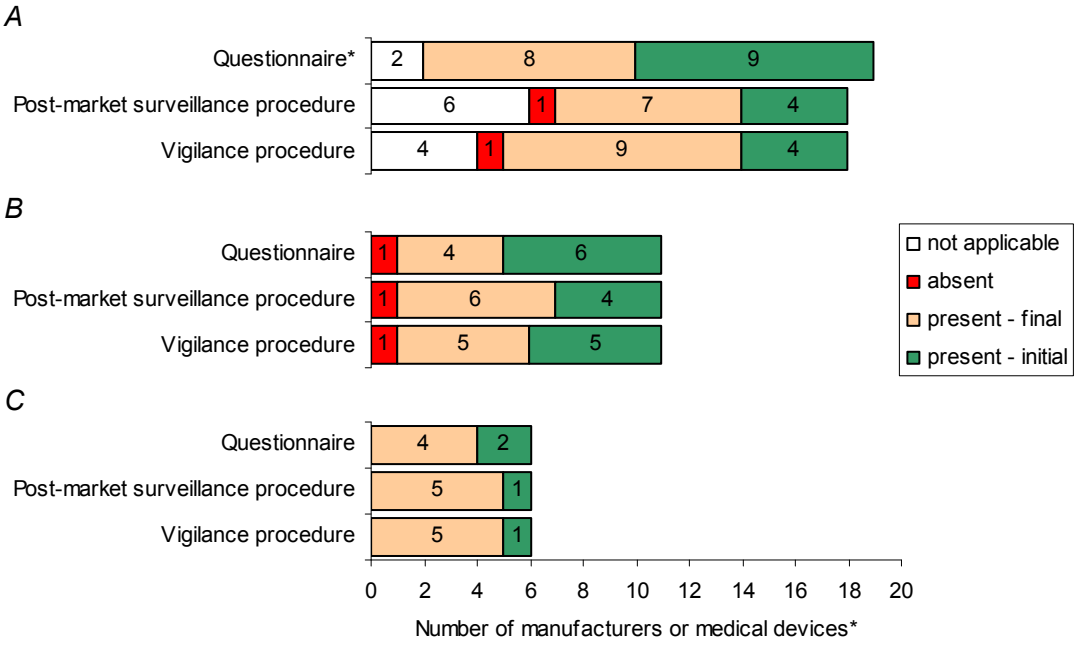

Figure A1. Availability of questionnaires and procedures concerning medical devices intended for clinical investigation (A), infusion pumps (B), and endoscope washer disinfectors (C).

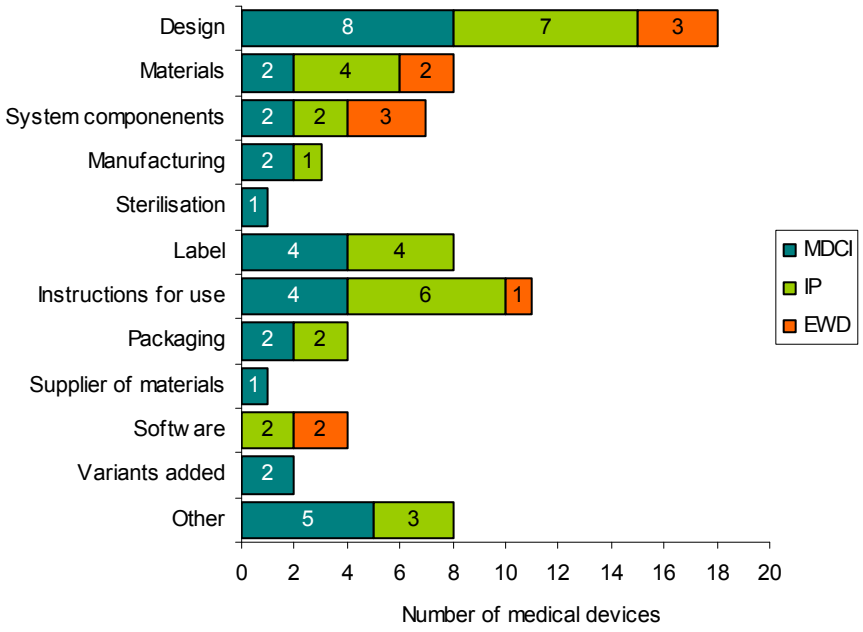

Figure A2. Nature of modifications to medical devices. Modifications are shown for product categories medical devices for clinical investigation (MDCI), infusion pumps (IP), and endoscope washer disinfectors (EWD).

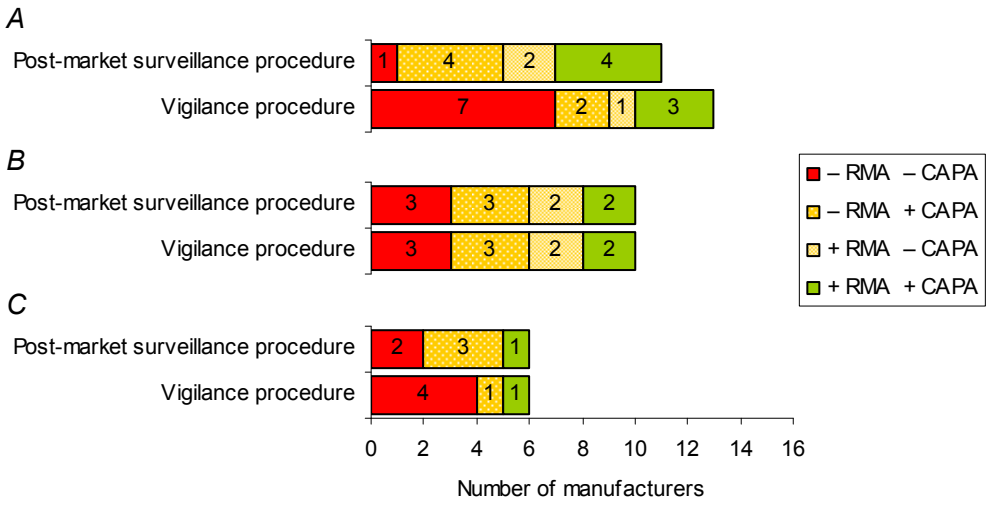

Figure A3. Relationship between risk management activities (RMA) and procedure for corrective and preventive action (CAPA). Presence of description of RMA en CAPA reference (indicated by +) in post-market surveillance and vigilance procedure are shown for medical devices intended for clinical investigation (A), infusion pumps (B), and endoscope washer disinfectors (C).

Appendix IV Tables

Table A1. Overview of data for product category concerning medical devices intended for clinical investigation

	Manufacturer ID																	
	1[o]	2[1]	3[2]	4	5[3]	6[†]	7[3]	8	9[a]	10[3]	11[2]	12[*]	13	14	15	16	17[o]	18	19
Availability																			
Questionnaire	p-f	p-i	p-f	p-i	p-f	na	p-i	p-f	p-i	p-i	p-f	na	p-f	p-i	p-i	p-i	p-f	p-i	p-f
PMS procedure	p-f	p-f	na	p-i	na	na	p-f	p-f	na	p-i	p-f	na	p-f	p-i	p-i	a	p-f	na	p-f
Vigilance procedure	p-f	p-f	na	p-i	p-f	na	p-f	p-f	na	p-i	p-f	na	p-f	p-i	p-i	a	p-f	p-f	p-f
Regulatory approval																			
CE-marked medical device	yes	no	no	yes	.	no	.	yes	no	yes	no	no	yes	yes	yes	yes	no	no	yes
Date of CE mark approval	Jan 2006	.	.	Jan 2008	§	.	.	Aug 2007	.	Feb 2006	.	.	Feb 2006	Aug 2006	Jul 2006	Mar 2007	.	‡	Aug 2007
Market release																			
Medical device on the market	yes	no	no	yes	.	no	.	yes	no	yes	no	no	yes	yes	yes	yes	no	no	no
Date of market release	Oct 2006	.	.	Feb 2008	.	.	.	Oct 2007	.	Sep 2006	.	.	Apr 2006	Jan 2007	Sep 2006	Apr 2007	.	‡	¶

[o] Different medical devices, but same manufacturer (CI #17 was ongoing).

[1] CI was ongoing.

[2] Medical device was inappropriate for market according to manufacturer. CI stopped early.

[3] Medical device was withdrawn from market. Commercialization discontinued due to economic and business reasons in May 2005 (#7) and May 2007 (#5). Manufacturers did not give information on the date of CE mark approval and market release.

† Manufacturer went out of business. CI stopped.

[a] CI concluded recently and finalization of the clinical study report was in process.

* Manufacturer was without European-authorised representative. Medical device was not on the European market.

§ Manufacturer received CE mark approval in February 2006 according to press release on manufacturer's website.

‡ CE mark approval was anticipated July 2008 (technical documentation was pending for CE mark approval with the notified body) and anticipated market release September 2008. Verification of the manufacturer's website in October 2008 could not confirm CE mark approval.

¶ Market release was anticipated May 2008. Verification of the manufacturer's website in October 2008 could not confirm market release.

Abbreviations: a (absent); CE (Conformité Européenne); CI (clinical investigation); ID (identification); na (not applicable); p-f (present – final); p-i (present – initial); PMS (post-market surveillance).

Table A2. Overview of data for product categories concerning infusion pumps and endoscope washer disinfectors

	Manufacturer ID										
	Infusion pumps										
	20	21	22	23	24	25	26	27	28	29	30
Availability											
Questionnaire	p-f	p-i	p-i	p-f	p-f	p-i	p-i	p-i	a	p-f	p-i
PMS procedure	p-f	p-i	p-i	p-f	p-f	p-f	p-i	p-f	a	p-f	p-i
Vigilance procedure	p-f	p-i	p-i	p-f	p-f	p-f	p-i	p-i	a	p-f	p-i

	Manufacturer ID					
	Endoscope washer disinfectors					
	31	32	33	34	35	36
Availability						
Questionnaire	p-i	p-i	p-f	p-f	p-f	p-f
PMS procedure	p-f	p-i	p-f	p-f	p-f	p-f
Vigilance procedure	p-f	p-i	p-f	p-f	p-f	p-f

Abbreviations: a (absent); ID (identification); na (not applicable); p-f (present – final); p-i (present – initial).

Table A3. Overview of data for product category concerning medical devices intended for clinical investigation

	Manufacturer ID																		
	1[o]	2[1]	3[2]	4	5[3]	6[†]	7[3]	8	9[a]	10	11[2]	12[*]	13	14	15	16	17[o]	18	19
Device modification-risk analysis interaction																			
Modification of medical device	yes	no	no	yes	no	.	yes	yes	yes	yes	no	.	yes	yes	no	no	yes	yes	no
Update of risk analysis	yes	no	no	yes	no	.	yes	yes	yes	yes	no	.	yes	yes	no	yes	yes	no	no
Reason for modification																			
CI finding / incidents during CI	no	na	na	yes	na	.	yes	yes	yes	no	na	.	no	no	na	na	yes	no	na
Post-market surveillance finding	no	na	na	na	na	.	na	no	na	no	na	.	no	yes	na	na	na	na	na
Vigilance finding (incidents)	no	na	na	na	na	.	na	no	na	no	na	.	no	no	na	na	na	na	na
Reason for risk analysis update																			
CI finding / incidents during CI	yes	na	na	yes	na	.	yes	yes	yes	no	na	.	no	no	na	no	yes	na	na
Post-market surveillance finding	yes	na	na	na	na	.	na	no	na	no	na	.	no	yes	na	no	na	na	na
Vigilance finding (incidents)	no	na	na	na	na	.	na	no	na	no	na	.	no	no	na	no	na	na	na
Device experience-modification relationship																			
Pre-market modification due to CI finding	no	yes	no	no	na	.	no	yes	un	yes	no	.	no	no	no	yes	yes	no	no
Pre-market modification due to CI incidents	no	un	no	yes	na	.	yes	yes	yes	un	no	.	na	un	no	un	un	no	na
Post-market modification due to PMS finding	no	na	na	na	no	.	na	na	na	yes	na	.	no	yes	no	no	na	na	na
Post-market modification due to incidents	no	na	na	na	no	.	na	na	na	no	na	.	no	no	no	no	na	na	na

[o] Different medical devices, but same manufacturer (CI #17 was ongoing).

[1] CI was ongoing.

[2] Medical device was inappropriate for market, CI stopped early.

[3] Medical device was withdrawn from market (#5 in May 2007, #7 in May 2005).

[†] Manufacturer went out of business.

[a] CI concluded recently.

* Manufacturer was without European-authorised representative, medical device not on market.

Abbreviations: CI (clinical investigation); ID (identification); na (not applicable); PMS (post-market surveillance); un (unknown).

Table A4. Overview of data for product category concerning medical devices intended for clinical investigation

	Manufacturer ID																		
	1º	2[1]	3[2]	4	5[3]	6†	7[3]	8	9[a]	10	11[2]	12*	13	14	15	16	17º	18	19
Nature of medical device modification																			
Design	yes	na	na	yes	na	.	yes	yes	yes	no	na	.	no	yes	na	na	yes	yes	na
Materials	no	na	na	no	na	.	no	yes	no	no	na	.	no	yes	na	na	no	no	na
System components	no	na	na	yes	na	.	no	yes	no	no	na	.	no	no	na	na	no	no	na
Manufacturing	no	na	na	yes	na	.	no	yes	no	no	na	.	no	no	na	na	no	no	na
Sterilisation	yes	na	na	no	na	.	no	no	no	no	na	.	no	no	na	na	no	no	na
Label	yes	na	na	no	na	.	no	yes	no	yes	na	.	yes	no	na	na	no	no	na
Instructions for use	yes	na	na	yes	na	.	no	yes	no	no	na	.	yes	no	na	na	no	no	na
Packaging	no	na	na	yes	na	.	no	yes	no	no	na	.	no	no	na	na	no	no	na
Supplier of materials	no	na	na	no	na	.	no	yes	no	no	na	.	no	no	na	na	no	no	na
Software	na	na	na	na	na	.	no	na	na	na	na	.	na	no	na	na	na	na	na
Variants added	yes	na	na	no	na	.	no	no	no	no	na	.	yes	no	na	na	no	no	na
Other	yes	na	na	yes	na	.	no	yes	no	yes	na	.	no	no	na	na	yes	no	na

º Different medical devices, but same manufacturer (CI #17 was ongoing).

[1] CI was ongoing.

[2] Medical device was inappropriate for market, CI stopped early.

[3] Medical device was withdrawn from market (#5 in May 2007, #7 in May 2005).

† Manufacturer went out of business.

[a] CI concluded recently.

* Manufacturer was without European-authorised representative, medical device not on market.

Abbreviations: CI (clinical investigation); ID (identification); na (not applicable); un (unknown).

Table A5. Overview of data for product categories concerning infusion pumps and endoscope washer disinfectors

	Manufacturer ID											Manufacturer ID					
	Infusion pumps											Endoscope washer disinfectors					
	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Device modification-risk analysis interaction																	
Modification of medical device	yes	yes	yes	yes	yes	yes	yes	yes	.	no	yes	yes	yes	no	yes	no	yes
Update of risk analysis	no	yes	yes	un	no	yes	no	yes	.	yes	yes	yes	no	yes	no	no	yes
Reason for modification																	
CI finding / incidents during CI	no	no	no	no	no	no	no	no	.	na	no	na	na	na	na	na	na
Post-market surveillance finding	no	yes	yes	yes	no	no	yes	no	.	na	yes	no	no	na	no	na	no
Vigilance finding (incidents)	no	no	no	no	no	no	no	no	.	na	yes	no	no	na	no	na	no
Reason for risk analysis update																	
Finding from CI / incidents during CI	na	no	no	na	na	no	na	no	.	no	no	na	na	na	na	na	na
Post-market surveillance finding	na	yes	no	na	na	yes	na	no	.	no	no	un	na	no	na	na	yes
Vigilance finding (incidents)	na	no	no	na	na	no	na	no	.	no	no	un	na	no	na	na	no
Device experience-modification relationship																	
Post-market modification due to PMS finding	yes	yes	yes	yes	no	no	yes	no	.	no	yes	no	yes	yes	na	yes	yes
Post-market modification due to incidents	no	na	na	yes	yes	no	no	no	.	no	yes	no	un	na	yes	no	yes

Abbreviations: ID (identification)); na (not applicable); PMS (post-market surveillance); un (unknown).

Table A6. Overview of data for product categories concerning infusion pumps and endoscope washer disinfectors

	Manufacturer ID											Manufacturer ID					
	Infusion pumps											Endoscope washer disinfectors					
	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Nature of medical device modification																	
Design	yes	yes	yes	yes	no	yes	yes	no	.	na	yes	no	yes	na	yes	na	yes
Materials	no	yes	no	no	no	yes	yes	no	.	na	yes	no	no	na	yes	na	yes
System components	no	yes	yes	no	no	no	no	no	.	na	no	no	yes	na	yes	na	yes
Manufacturing	no	no	no	no	no	no	yes	no	.	na	no	no	no	na	no	na	no
Sterilisation	no	no	no	no	no	no	no	no	.	na	no	no	no	na	no	na	no
Label	no	no	yes	no	yes	no	yes	yes	.	na	no	no	no	na	no	na	no
Instructions for use	no	yes	yes	no	yes	yes	yes	no	.	na	yes	no	no	na	yes	na	no
Packaging	no	no	no	no	no	yes	no	no	.	na	yes	no	no	na	no	na	no
Supplier of materials	no	no	no	no	no	no	no	no	.	na	no	no	no	na	no	na	no
Software	no	no	no	yes	yes	no	no	no	.	na	no	yes	no	na	yes	na	no
Variants added	no	no	no	no	no	no	no	no	.	na	no	no	no	na	no	na	no
Other	no	no	no	yes	yes	no	no	no	.	na	yes	no	no	na	no	na	no

Abbreviations: ID (identification)); na (not applicable); un (unknown).

Table A7. Overview of data for product category concerning medical devices intended for clinical investigation

	Manufacturer ID																		
	1º	2[1]	3[2]	4	5[3]	6†	7[3]	8	9[a]	10	11[2]	12*	13	14	15	16	17º	18	19
Current PMS procedure																			
Active customer feedback	yes	no	na	no	na	.	no	no	na	yes	yes	.	yes	yes	yes	.	.	na	no
Passive customer feedback	yes	yes	na	yes	na	.	yes	yes	na	yes	no	.	yes	yes	yes	.	.	na	yes
Post-market clinical follow-up	yes	no	na	no	na	.	no	no	na	yes	no	.	yes	yes	no	.	.	na	no
Literature review	no	no	na	no	na	.	yes	yes	na	yes	no	.	yes	yes	yes	.	.	na	no
Risk management activities	no	yes	na	no	na	.	yes	yes	na	yes	no	.	yes	no	yes	.	.	na	no
CAPA procedure	no	no	na	yes	na	.	yes	yes	na	no	yes	.	yes	yes	yes	.	.	na	yes
Document responsibility	yes	yes	na	yes	na	.	yes	yes	na	yes	no	.	yes	yes	yes	.	.	na	yes
Date of issue	.	Sep 2007	.	Jun 2007	.	.	Mar 2008	Dec 2007	.	Jan 2006	Dec 2006	.	May 2005	Jun 2006	Sep 2006	.	.	.	.
Previous PMS procedure																			
Active customer feedback	yes	.	no	no	.	.	no	no	.	yes	yes	yes	.	no	no	.	.	.	.
Passive customer feedback	yes	.	yes	yes	.	.	yes	yes	.	yes	no	yes	.	yes	yes	.	.	.	.
Post-market clinical follow-up	yes	.	no	no	.	.	no	no	.	no	no	no	.	yes	no	.	.	.	.
Literature review	no	.	no	no	.	.	yes	yes	.	yes	yes	yes	.	yes	no	.	.	.	.
Risk management activities	no	.	no	no	.	.	yes	yes	.	yes	no	no	.	no	no	.	.	.	.
CAPA procedure	no	.	no	no	.	.	yes	yes	.	no	yes	yes	.	yes	yes	.	.	.	.
Document responsibility	no	.	yes	yes	.	.	yes	no	.	yes	no	yes	.	yes	yes	.	.	.	.
Date of issue	.	.	Jul 2005	Oct 2000	.	.	May 2005	Mar 2005	.	.	May 2002	Feb 2005	¶	Dec 2005	Nov 2004	.	.	.	¶
Implementation of PMS activities																			
Active customer feedback	un	na	na	na	no	.	no	na	na	no	na	.	no	no	un	un	na	na	na
Passive customer feedback	un	na	na	na	yes	.	no	na	na	yes	na	.	no	yes	un	un	na	na	na
Post-market clinical follow-up	yes	na	na	na	no	.	no	na	na	yes	na	.	yes	no	un	un	na	na	na
Literature review	un	na	na	na	no	.	no	na	na	no	na	.	no	no	un	no	na	na	na

º Different medical devices, but same manufacturer (CI #17 was ongoing).

[1] CI was ongoing.

[2] Medical device was inappropriate for market, CI stopped early.

[3] Medical device was withdrawn from market (#5 in May 2007, #7 in May 2005).

† Manufacturer went out of business.

[a] CI concluded recently.

* Manufacturer was without European-authorised representative, medical device not on market.

¶ Previous and current procedure had identical content (#13, #19) and date of issue (#13).

Abbreviations: CAPA (corrective and preventive action); CI (clinical investigation); ID (identification); na (not applicable); PMS (post-market surveillance); un (unknown).

Table A8. Overview of data for product categories concerning infusion pumps and endoscope washer disinfectors

	Manufacturer ID											Manufacturer ID					
	Infusion pumps											Endoscope washer disinfectors					
	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Current PMS procedure																	
Active customer feedback	yes	yes	yes	no	yes	no	yes	no	.	yes	yes	yes	yes	no	no	yes	yes
Passive customer feedback	yes	yes	yes	yes	no	yes	yes	yes	.	yes	yes	yes	yes	yes	yes	yes	no
Post-market clinical follow-up	no	yes	yes	no	no	no	no	no	.	no	no	na	na	na	na	na	na
Literature review	yes	yes	yes	no	yes	no	yes	no	.	yes	yes	no	no	no	no	yes	no
Risk management activities	no	no	yes	yes	no	no	no	yes	.	yes	no	no	no	yes	no	no	no
CAPA procedure	yes	yes	yes	no	no	no	yes	yes	.	no	no	yes	no	yes	yes	no	yes
Document responsibility	yes	yes	yes	no	yes	yes	yes	yes	.	yes	yes	no	yes	yes	yes	no	no
Date of issue	Nov 2007	Dec 2007	Aug 2005	Aug 2007	Oct 2006	Feb 2008	‡	Oct 2007	.	Mar 2007	Nov 2007	.	Feb 2008	Jul 2007	Aug 2006	.	Dec 2003
Previous PMS procedure																	
Active customer feedback	.	.	.	.	yes	.	yes	no	.	no	.	.	.	.	.	.	.
Passive customer feedback	.	.	.	.	yes	.	yes	yes	.	yes	.	.	.	.	.	.	.
Post-market clinical follow-up	.	.	.	.	yes	.	no	no	.	no	.	.	.	.	.	.	.
Literature review	.	.	.	.	yes	.	yes	no	.	no	.	.	.	.	.	.	.
Risk management activities	.	.	.	.	yes	.	no	yes	.	no	.	.	.	.	.	.	.
CAPA procedure	.	.	.	.	no	.	yes	yes	.	no	.	.	.	.	.	.	.
Document responsibility	.	.	.	.	yes	.	yes	yes	.	no	.	.	.	.	.	.	.
Date of issue	.	.	¶	.	Jun 2005	.	‡	Feb 2005	.	.	.	.	.	.	.	.	.
Implementation of PMS activities																	
Active customer feedback	un	yes	un	no	un	un	no	un	.	no	yes	yes	un	no	na	un	un
Passive customer feedback	un	yes	yes	yes	un	un	yes	un	.	yes	yes	no	un	yes	na	un	un
Post-market clinical follow-up	un	no	no	na	na	na	na	na	.	na	na	na	na	na	na	na	na
Literature review	un	no	no	no	un	un	no	un	.	no	no	no	un	no	na	un	no

¶ Current and previous procedure had identical content and date of issue.

‡ Current procedure: document version 04. Previous procedure: document version 02.

Abbreviations: CAPA (corrective and preventive action); ID (identification); na (not applicable); PMS (post-market surveillance); un (unknown).

Table A9. Overview of data for product category concerning medical devices intended for clinical investigation

	Manufacturer ID																		
	1°	2[1]	3[2]	4	5[3]	6†	7[3]	8	9[a]	10	11[2]	12*	13	14	15	16	17°	18	19
Current vigilance procedure																			
Incident reporting	yes	yes	na	yes	yes	.	yes	yes	na	yes	yes	.	yes	yes	yes	.	.	yes	yes
Notification to competent authority	yes	yes	na	yes	yes	.	yes	yes	na	yes	yes	.	yes	yes	yes	.	.	yes	yes
Risk management activities	no	yes	na	no	no	.	yes	no	na	no	no	.	yes	no	no	.	.	no	no
CAPA procedure	no	no	na	no	no	.	yes	no	na	no	yes	.	yes	no	yes	.	.	no	yes
MEDDEV Guidelines 2.12-1 rev 5 (2007)	yes	yes	na	no[n]	no[n]	.	no‡	yes	na	no‡	no‡	.	no[n]	no§	no	.	.	yes	no§
FSCA principle (recall)	yes	no	na	yes	no	.	yes	yes	na	no	no	.	yes	no	yes	.	.	yes	yes
Document responsibility	yes	yes	na	yes	yes	.	yes	yes	na	yes	no	.	yes	yes	no	.	.	yes	yes
Date of issue	Dec 2007	Sep 2007	.	Nov 2006	Dec 2007	.	Mar 2008	Sep 2007	.	Oct 2007	Aug 2007	.	May 2005	May 2007	Dec 2007	.	.	Jul 2007	.
Previous vigilance procedure																			
Incident reporting	yes	.	yes	yes	yes	.	yes	yes	.	yes	yes	yes	.	yes	yes	.	.	yes	.
Notification to competent authority	yes	.	yes	yes	yes	.	yes	yes	.	yes	yes	yes	.	yes	yes	.	.	yes	.
Risk management activities	no	.	no	no	no	.	yes	yes	.	no	no	no	.	no	no	.	.	no	.
CAPA procedure	no	.	no	no	no	.	yes	yes	.	no	yes	yes	.	no	no	.	.	no	.
MEDDEV Guidelines 2.12-1 rev 4 (2001)	yes	.	no‡	yes	no§	.	no‡	yes	.	no[4]	no‡	no	.	no	no‡	.	.	no	.
Recall (FSCA principle)	no	.	yes	yes	no	.	yes	yes	.	no	no	yes	.	yes	yes	.	.	no	.
Document responsibility	no	.	yes	yes	yes	.	yes	no	.	yes	no	yes	.	yes	yes	.	.	no	.
Date of issue	.	.	Jul 2005	Mar 2005	Apr 2005	.	May 2005	Mar 2005	.	Apr 2003	Nov 2005	Feb 2005	¶	Nov 2005	Sep 2003	.	.	.	¶
Merger of current procedures																			
Post-market surveillance and vigilance	no	yes	na	no	na	.	yes	no	na	no	no	.	yes	no	no	.	no	na	yes

° Different medical devices, but same manufacturer (CI #17 was ongoing).

[1] CI was ongoing.

[2] Medical device was inappropriate for market, CI stopped early.

[3] Medical device was withdrawn from market (#5 in May 2007, #7 in May 2005).

† Manufacturer went out of business.

[a] CI concluded recently.

* Manufacturer was without European-authorised representative, medical device not on market.

[n] MEDDEV 2.12-1 rev 4 (April 2001).

§ No previous or current MEDDEV guidance mentioned.

‡ MEDDEV reference was incomplete, i.e. year of publication and revision number of procedure were omitted.

[4] MEDDEV 2.12-1 rev 3 (March 1998).

¶ Previous and current procedure had identical content (#13, #19) and date of issue (#13).

Abbreviations: CAPA (corrective and preventive action); FSCA (field safety corrective action); ID (identification); na (not applicable).

Table A10. Overview of data for product categories concerning infusion pumps and endoscope washer disinfectors

	Manufacturer ID											Manufacturer ID					
	Infusion pumps											Endoscope washer disinfectors					
	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Current vigilance procedure																	
Incident reporting	yes	yes	yes	yes	yes	yes	yes	yes	.	yes	yes	yes	yes	yes	yes	yes	yes
Competent authority notification	yes	yes	yes	yes	yes	yes	yes	yes	.	yes	yes	yes	yes	yes	yes	yes	yes
Risk management activities	no	no	no	no	yes	yes	no	yes	.	no	yes	yes	no	no	no	no	no
CAPA procedure	yes	yes	no	no	yes	no	yes	yes	.	no	no	yes	no	no	yes	no	no
MEDDEV Guideline 2.12-1 rev 5 (2007)	no[o]	yes	yes	no[1]	no[o]	no[2]	no[2]	no[1]	.	no[2]	yes	no[1]	no[3]	no[o]	no[o]	no[1]	yes[a]
FSCA principle (recall)	yes	yes	yes	no	yes	no	yes	yes	.	yes	yes	yes	yes	no	yes	yes	yes
Document responsibility	yes	yes	yes	yes	yes	yes	yes	yes	.	yes	yes	no	yes	yes	yes	no	yes
Date of issue	Nov 2007	Sep 2007	Nov 2007	Feb 2006	Jan 2008	Jan 2007	‡‡	Sep 2003	.	Jul 2003	Nov 2007	Jun 2006	Sep 2005	Aug 2006	Feb 2006	.	.
Merger of current procedures																	
Post-market surveillance and vigilance	no	no	no	no	no	no	yes	no	.	no	yes	no	no	no	yes	no	no

[o] MEDDEV 2.12-1 rev 4 (2001).

[1] No current and previous MEDDEV guidance mentioned.

[2] MEDDEV reference incomplete, i.e. revision number and year of publication omitted.

[3] MEDDEV 3/93 rev 4.

[a] Version of the MEDDEV guidance not mentioned. Instead procedure referred to EC website for current MEDDEV version.

‡ Current procedure: document version 04.

Abbreviations: CAPA (corrective and preventive action); FSCA (field safety corrective action); ID (identification); na (not applicable); un (unknown).

Table A11. Previous and current post-market surveillance and vigilance procedures

	Date of previous procedure		Date of current procedure		Difference current – previous
	Mean (n)	Range	Mean (n)	Range	Mean ± SD (n)
Post-market surveillance procedure					
Medical devices intended for CI	May 2004 (8)	Oct 2000 – Dec 2005	Dec 2006 (9)	May 2005 – Mar 2008	38 ± 26 months (6)
Infusion pumps	Apr 2005 (2)	Feb 2005 – Jun 2005	May 2007 (9)	Aug 2005 – Feb 2008	24 months (2)
Endoscope washer disinfectors	-	-	Jul 2006 (4)	Dec 2003 – Feb 2008	-
All medical devices	Jul 2004 (10)	Oct 2000 – Dec 2005	Jan 2007 (22)	Dec 2003 – Mar 2008	35 ± 23 months (8)
Vigilance procedures					
Medical devices intended for CI	Jan 2005 (10)	Apr 2003 – Nov 2005	Jun 2007 (12)	May 2005 – Mar 2008	33 ± 14 months (8)
Infusion pumps	-	-	Aug 2006 (9)	Jul 2003 – Jan 2008	-
Endoscope washer disinfectors	-	-	Apr 2006 (4)	Sep 2005 – Aug 2006	-
All medical devices	Jan 2005 (10)	Apr 2003 – Nov 2005	Dec 2006 (25)	Jul 2003 – Mar 2008	33 ± 14 months (8)

Abbreviations: CI (clinical investigation)

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