

# **Poly Implant Prothèse (PIP) silicone breast implants**

*Review of the actions of the Medicines and  
Healthcare products Regulatory Agency  
(MHRA) and Department of Health*

## Poly Implant Prothèse (PIP) silicone breast implants

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*Review of the actions of the Medicines and Healthcare products Regulatory Agency (MHRA) and the Department of Health*

Prepared by the Department of Health

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# Glossary

**ABS** – the Association of Breast Surgery, “representing healthcare professionals treating malignant and benign breast disease, focussing on education, audit and guidelines...to enhance the treatment of patients with breast disease”.

**Adverse device incident** (for reporting purposes) - any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or instructions for use which, directly or indirectly might lead to or have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.’ In this instance a ‘serious deterioration’ in the state of someone’s health can include:

- a life-threatening illness
- permanent impairment of a body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent either of the first two criteria (this includes increase duration of surgery and conditions requiring hospitalisation or prolongation of existing hospitalisation)
- indirect harm as a consequence of an incorrect diagnostic result
- foetal distress, foetal death or any congenital abnormality or birth defect.

**AFSSAPS** – Agence Française de Sécurité Sanitaire des Produits de Santé. The French competent authority responsible for regulation of medicines and medical devices (equivalent of the MHRA).

**ALCL** – Anaplastic Large Cell Lymphoma. A rare type of lymphoma (cancer of the lymphatic system) usually involving T-cells growing in an uncontrolled way. A possible association between ALCL and breast implants in general (ie not PIP specifically) has been identified, but there are insufficient data to determine if the association is real due to the very rare nature of ALCL including in women with breast implants.

**BAAPS** – the British Association of Aesthetic Plastic Surgeons. Association “established for the advancement of education in, and the practice of, Aesthetic Plastic Surgery for public benefit”.

**BAPRAS** – British Association of Plastic, Reconstructive and Aesthetic Surgeons. Professional association that “exists to promote the best evidence-based practice in plastic, reconstructive and aesthetic surgery in order to achieve the highest standard of patient care through professional support in education, research and the development of knowledge”.

**Breast implant** – a medical prosthesis used in post–mastectomy breast reconstruction or for breast augmentation.

**Breast Implant Group (BIG)** – Internal MHRA group who consider breast implant related issues. The group generally comprises the Medical Devices Specialists with responsibility for breast implant incident reports, the head of the Biosciences and Implants Unit, team manager of the Biosciences and Implants Unit Orthopaedic Group, and the MHRA Clinical Director. The frequency of BIG meetings varies widely over the period covered by this review, from monthly to yearly.

**Breast Implant Registry** – a voluntary registry of breast implant usage in the UK which was operated from 1995 to 2005. It was shut down due to a high proportion of women not consenting to their details being recorded, meaning the information the registry contained was of inadequate quality for research purposes.

**CE mark** – Conformité Européenne mark that signifies a product meets the accepted standards of safety.

**Central Alerting System (CAS)** – a web-based system for issuing patient safety alerts, medical device alerts, public health notices and other safety critical guidance to the NHS. It enables alerts to be emailed to key contacts across the health care system and allows the onward cascading of this information to relevant health care workers. It also provides a web portal for accessing relevant information.

**Cohesive** – in relation to silicone breast implants, ‘cohesive’ refers to the extent to which the silicone polymer molecules making up the implant filler gel are ‘cross-linked’, or joined to each other. A ‘high cohesive’ gel has a relatively higher proportion of cross-linked molecules and is more rigid, while a ‘low cohesive’ gel has relatively fewer cross-links and is therefore more fluid.

**Committee on the Safety of Devices (CSD)** – committee of independent experts established to support the MHRA in ensuring that medical devices and equipment meet appropriate standards of safety, quality and performance by giving advice on a range of device related initiatives.

**Competent Authority** – national body responsible for the compliance with and enforcement of the EU Medical Devices Directive as it applies to medical devices, device manufacturers and Notified Bodies in their Member State. In the UK this is the MHRA.

**Device Specialist** (at the MHRA) – Member of MHRA staff, with a scientific or other relevant qualification, responsible for investigating device adverse incidents and developing safety advice.

**Explantation** – the process of surgically removing an implant from a person.

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**FDA** – the United States Food and Drug Administration. The US regulator for medical devices, medicines and a range of other products.

**Genotoxicity** – the ability of a substance or type of energy to have a harmful effect on the integrity of genetic material, rendering them potentially carcinogenic (able to cause cancer) or mutagenic (able to cause mutations in genes).

**Hampton principles** – a set of principles for high quality and proportionate regulation produced by Sir Philip Hampton in his review of regulation in 2005.

**Hydrogel** – a type of breast implant filler consisting of a network of polymer chains that absorb water. PIP were using a hydrogel implant filler material until December 2000 when MDA (now MHRA) issued a Medical Device Alert for the voluntary recall by PIP of their hydrogel breast implants. PIP voluntarily withdrew hydrogel implants from sale due to a lack of testing information regarding the safety of hydrogel as an implant filler. MDA'S alert stated that 'The manufacturer has, as a precautionary measure, voluntarily withdrawn PIP hydrogel breast implants from the UK market until sufficient information to address MDA's concerns is available. Women who are worried should be offered a consultation. It should be emphasised that a definite risk has not been identified.'

**IMGHC** – 'High Cohesive Gel Mammary Implant' (translated from French) – overall model name for PIP silicone gel filled breast implants that are the focus of concerns regarding the composition of the silicone gel filler material. The majority of the models sold in the UK are the textured shell version or IMGHC-TX models.

**Implantation** – the process of surgically inserting an implant into a person.

**Irritant** – a substance that causes irritation, which is a state of inflammation or painful reaction to that substance, sometimes caused by an allergic response or due to the body's non-specific attempt to remove the irritant.

**MDA – Medical Devices Agency** – the predecessor to the MHRA with responsibility for medical device safety and regulation.

**MDA – Medical Devices Alert** – notice issued by MHRA with important safety information related to a medical device sent to key contacts across the healthcare system using the Central Alerting System with instructions for further cascading to relevant health care workers, as well as being posted on the MHRA website.

**Medical Device** – defined in European law as “any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings.”

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**MDEG** – Medical Device Expert Group. Established by the EU Commission, MDEG is composed of delegates from member state competent authorities, industry and other stakeholder representatives in the area of medical devices and is the forum in which the implementation of the Medical Devices Directive is discussed. In closed session, MDEG consists of member state competent authorities only and is a forum to discuss all issues relating to the implementation of the medical device directives. MDEG is responsible for publishing guidance documents which reflect the consensus position of its members on interpretation of the Medical Devices Directive.

**Medical Device Liaison Officers** - members of staff designated in all NHS trusts and primary care trusts in England who are responsible for encouraging effective and comprehensive adverse incident reporting through encouragement and training of healthcare and support staff and medical device users.

**Medical Devices Directives** – European Union legislation which, when translated into national law in EU member states, provides the legal framework for regulation of medical devices in Europe.

**MHRA** – the Medicines and Healthcare products Regulatory Agency, the UK competent authority responsible for regulation of medicines and medical devices. MHRA is an Executive Agency of the Department of Health.

**Notified Body** – third-party private sector organisations designated by their national Competent Authority and commissioned by manufacturers to determine whether a particular medical device meets the relevant regulatory requirements and, whether, when used as intended, it works properly and is acceptably safe (the process known as conformity assessment).

**NBOG** – Notified Body Operations Group. A group established by the EC and member states to “improve the overall performance of notified bodies in the medical devices sector by primarily identifying and promulgating examples of best practice to be adopted by both notified bodies and those organisations responsible for their designation and control.” NBOG membership consists of the European Commission and nominees from the member states’ designating/competent authorities. Additionally, membership of the Group is open to EFTA/EEA competent authorities as well as candidate and accession countries. On the whole, members of the Group are nominated by their competent authorities on the basis of their expertise in the area of notified body designation and control.

**NuSil** – International silicone materials manufacturing company based in California who provided the approved silicone raw components that were meant to be used by PIP to manufacture the filler (NuSil gel) for PIP’s silicone implants. Investigation by AFSSAPS has revealed PIP were using NuSil silicone components to manufacture fillers for some implants, but that they were also using raw materials sourced from other companies (Bluestar and Momentive) that were not intended for medical use to make their own formulation of silicone filler material.

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**Patch** – a section of shell used to cover the hole in the main implant shell through which the shell is filled with implant filler. The patch was glued to the main shell in PIP's silicone implants.

**PIP** - Poly Implant Prothèse. Manufacturer of various breast implants, including silicone gel-filled implants, which were found by AFSSAPS to be filled with an unapproved silicone filler.

**Post-market surveillance** – a systematic procedure to review experience gained from their devices after they are placed on the EU market, 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:

- (a) any adverse incident which might lead to or might have led to the death of a patient or user or to a serious deterioration in their state of health;
- (b) any field safety corrective action (e.g. systematic recall) undertaken by the manufacturer to reduce the risk of adverse incidents with the device.

**Rupture** – damage to the shell of a breast implant leading to the integrity of the implant being compromised and the potential for implant filler to leak from the implant.

**Saline** – biological concentration salt (sodium chloride) solution used to fill some breast implants, including some PIP models.

**Shell** – The envelope or 'bag' that forms the exterior of a breast implant, generally made from an elastic material such as silicone elastomer.

**Silent rupture** – the rupture of a breast implant inside a person but where there are no obvious signs or symptoms such as pain, lumps or changes in breast shape or feel, often because the filler does not migrate or change shape.

**Silicone** – polymeric compounds of silicon-containing monomers with generally low toxicity and reactivity, and high stability, used for a variety of purposes, including medical ones. The extent of cross-linking of the polymerised molecules determines the rigidity of the silicone. A number of companies use silicone as a filler for their breast implants, with those with a higher number of cross-links leading to a more rigid silicone gel being referred to a 'high-cohesive' silicone implants.

**TGA** – Therapeutic Goods Administration. Australian regulator for medicines and medical devices.

**Time to rupture** – the length of time from a breast implant being put inside a person to the point at which it ruptures. This can be expressed as an average (mean) time to rupture for a batch or type of implant.

**Toxicology** – the scientific study of the effects and characteristics of poisons.

**Trending/Trend Analysis** – analysis of data relating to the frequency and characteristics of all adverse device incidents reported involving a particular batch, brand or type of medical device

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in order to identify any particular concerns with the safety of that batch, brand or type of device (as opposed to analysis of a single adverse device incident).

**Trilucent** – Brand name of a type of breast implant filled with soya bean oil, manufactured by Lipomatrix. These were withdrawn from sale in 1999 when it became clear that the soya bean oil was producing toxic by-products in implanted women. Women with these implants were advised to have them removed because of the risks to their health.

**TUV Rheinland** – German notified body that issued the certificate that approved the use of the CE mark for PIP silicone breast implants.

**Vigilance** – In the context of the EC Medical Devices Directive this refers to:

- a) the part of manufacturers' post-market surveillance system that obliges them to report and investigate adverse incidents involving actual or potential serious deterioration in state of health to the relevant competent authorities, and to inform Competent authorities of any field safety corrective actions being undertaken to reduce the risk of adverse incidents
- b) to the system of post-market surveillance administered by a Member State's competent authority to collate and examine adverse incident reports and other information regarding device safety from manufacturers and users, and take any measures necessary to minimise the recurrence of the adverse incidents.

# Executive summary

The worry and distress caused by the fraudulent activities of PIP, the French manufacturer of breast implants, have placed a huge burden on the lives of many UK women. The fact that PIP deliberately concealed their use of a non-approved filler material has rightly triggered questions about how this can have happened, and how it remained undetected for such a long period. We owe it to the thousands of affected women to learn any lessons that can help us offer the best protection to anyone who receives breast implants, or other kinds of medical implant, in the future.

In conducting this review, I have therefore sought to determine whether the actions of the UK regulator, the MHRA, and the UK Government, could have reasonably prevented or alleviated this considerable distress, or indeed uncovered the fraud earlier.

The review has considered the available evidence on MHRA and DH action relating to PIP breast implants up to 24 December 2011. The evidence detailed in this report shows that the MHRA was fulfilling its obligations in terms of reviewing and responding to the incidents reported to them involving PIP breast implants. The MHRA was active in pursuing PIP about incidents involving its implants. Its focus was on determining if there were underlying problems with the implants, or if the incidents reported were the expected result of the widespread use of a type of device that has a tendency to fail over time.

However, it is also clear that these investigations were hampered by a lack of reliable and comprehensive information about all the adverse incidents relating to PIP breast implants, as well as uncertainty about comparative data on similar products. The MHRA was attempting to draw evidence-based conclusions about the performance of a device from data that were incomplete, and which we now know were filtered through a manufacturer that turned out to be fraudulent, while working on the assumption that all parts of the system were acting in good faith. The MHRA also had to rely on assurances from other official agencies responsible for inspecting the manufacturer and approving the device in question.

I have looked carefully at whether there were specific occasions over the last decade where the MHRA could have acted differently, for example by pursuing more vigorously additional information from surgeons who had reported incidents with PIP implants. The evidence shows MHRA did take these concerns into account, along with reported information on adverse incidents. In 2007 it referred concerns about PIP's handling of adverse incidents to the German notified body with responsibility for assessing PIP – TÜV Rheinland – and was reassured by that body that they had looked into these concerns, leading PIP to improve their practices. There was no reason for the MHRA not to accept that reassurance.

The MHRA continued to analyse PIP incident data after the reassurance from the German notified body. These data were not conclusive about a problem with PIP implants, but did suggest that a small number of PIP implants were failing more quickly than other types of

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implant. MHRA continued to pursue these concerns actively until the point in March 2010 when the French regulator inspected the manufacturer and discovered the use of non-approved filler material.

Up until March 2010, there was no evidence available to the MHRA that PIP were not using the filler they were supposed to be. Nor have we heard any suggestion that other European regulators had any such evidence or suspicion. All suspicions related to a possible tendency for early rupture of some implants, perhaps associated with the manufacture of the implant shell. Given the lack of data on the performance of these implants over time, it is still not clear to what extent PIP implants fail more frequently, or earlier, than expected.

Looking closely at the response of the MHRA to the French regulator's discovery, I have found no evidence that the MHRA acted inappropriately. It rightly issued an alert notice and other communications to surgeons and the public regarding the problem with PIP filler, halted use of the implants in the UK, and tried to work with European and other international regulators to determine what the safety implications were, providing further information as it became available.

When it became clear that the results of French toxicology tests would be unacceptably delayed, the MHRA immediately commissioned its own testing and was able to provide reassuring information to UK women weeks or months earlier than would otherwise have been the case.

I have seen evidence of the MHRA's discussions with toxicology experts, clinical advisers and relevant professional bodies. This demonstrates it was using evidenced-based and scientifically rigorous advice to draw up its advice to clinicians and the public. The MHRA's scientific advice was endorsed by Sir Bruce Keogh's expert group in its interim report on 6 January 2012.

There are however lessons to learn and areas where improvements can and should be made for the future. Adverse incident reporting is an inherently imperfect way of collecting data. It relies upon all those involved in delivering care - clinicians, cosmetic surgery providers, and manufacturers - playing their part in full and acknowledging the importance of adverse incident reporting in protecting patient safety. All those involved must redouble their efforts to improve reporting of incidents and ensure that information is shared with the MHRA. Even then, reporting will never reflect 100% of the experience with a device and this means other information must be generated and used.

The MHRA must be able to obtain evidence from a wider and more detailed set of sources, including robust outcomes data from clinicians. It needs to be at the forefront of using more sophisticated and rich sources of data to determine if there are problems with a device. It must have the ability to review routinely the sum total of the information about specific higher-risk devices, to ensure that the need for any further action is identified promptly.

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Difficult decisions had to be taken about communications following the discovery that an unauthorised filler had been used in PIP implants. The MHRA had to balance the need to provide full information against the risk of causing undue concern to women when they did not have clear evidence of potential harm. Government ministers followed the advice of the MHRA and other clinical experts, and the review finds no evidence to suggest that the wrong decisions were made based on what was known at the time. However the MHRA and Department of Health must learn lessons so that they can continue to improve their approach to communicating with affected individuals and the general public, particularly around issues that cause such understandable anxiety. We need to ensure that full, clear and accurate information is made available promptly in a way that is easily accessible and reflects the concerns that weigh so heavily on the lives of individuals who are affected by doubts over the safety of specific medical devices.

It is clear that there is also scope for all EU countries to work more closely together and get better at sharing information on devices, and this can and should be done within the existing regulatory framework. We must in addition work to ensure that the ongoing revision of the European regulation of devices ensures the system works robustly and that information sharing across international boundaries is comprehensive, timely and accurate.

Nothing about this case provides evidence to suggest the system for regulating medical devices is fundamentally unsound and that there needs to be a shift to a system like that used to regulate pharmaceuticals in the EU, or the system used to regulate higher risk devices in the United States. Very simply, PIP applied for and received approval for their silicone breast implant and then, after receiving approval, fraudulently changed the device to use a non-approved filler material. Putting in place even the most exhaustive testing regime before market authorisation would not have prevented this deliberate fraud taking place once the product was on the market.

Ultimately the responsibility for the great distress caused to UK women, and indeed many thousands of women worldwide, lies squarely with the fraudulent manufacturer who actively covered up its deceit and showed a complete disregard for the welfare of its customers. There is no evidence in relation to PIP implants that the MHRA or the wider Department of Health significantly failed to do their job. But they must learn lessons to help provide a stronger assurance for patients and the public that the device regulatory system is working to safeguard their health.

We are committed to supporting women in the UK who are victims of this situation, and to learning what lessons we can to improve the working of the wider regulatory system. Working with our European partners, we must ensure there are effective deterrents to undertaking this kind of fraud, and that the regulatory bodies are as well-equipped as possible to investigate any concerns they have, to ensure such fraud is detected and punished. A further review chaired by Professor Sir Bruce Keogh is examining wider issues around the regulation of cosmetic surgery, with a strong focus on what more can be done to protect the interests of patients, and this report also highlights issues his work should address.

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**Earl Howe**

**Parliamentary Under Secretary of State for Quality**

**Department of Health**

## Recommendations

**Recommendation i:** *There is a system-wide responsibility for maximising reporting of adverse device incidents and for ensuring that reports are of high quality. The MHRA should continue to work with health providers, professional bodies, regulators and patient groups to promote the best possible understanding of the role of the reporting system and to ensure that professionals in particular understand what they have a duty to report – and why.*

**Recommendation ii:** *The MHRA should work with partners to explore the potential for strengthening the network of Medical Device Liaison Officers, and emphasising the importance of the role within health care providers. In particular, it should work with the main private health care providers to encourage the establishment of a network of Medical Device Liaison Officers in that sector to complement that which exists in the NHS.*

**Recommendation iii:** *The MHRA should press ahead with planned work to improve its periodic trend analysis of data on adverse device events, including a more systematic focus on analysis of the rate of reported incidents relative to sales. This work should incorporate provision for periodic expert, external statistical input to support analysis of the available data on adverse device events and help identify what other data are needed. It should include consideration of how best to use additional sources of information alongside incident reporting to assist in the early identification of issues.*

**Recommendation iv:** *While acknowledging that a “one size fits all” approach to consideration of cumulative vigilance information will never be appropriate given the wide diversity of medical devices on the market, the MHRA should ensure that it has clear operating procedures for the periodic review of ongoing series/categories/types of device incident reports, particularly for higher risk products, including appropriate involvement of external experts. Plans to involve members of the Committee on Safety of Devices in such activity should be implemented without delay.*

**Recommendation v:** *The MHRA should review the way in which it manages records and knowledge on ongoing device issues so that they can be retrieved and analysed more easily for the purposes of retrospective review and learning, and the construction of narrative information to support the periodic review procedures mentioned above.*

**Recommendation vi:** *The MHRA should review the processes and governance it uses to ensure that timely and appropriate action is taken in pursuing responses from manufacturers, notified bodies or others, and in ensuring appropriate regulatory actions take place in a timely manner.*

**Recommendation vii:** *Sir Bruce Keogh’s review should examine ways of promoting a stronger culture of clinical governance, clinical audit and reporting in cosmetic surgery. Routine incident*

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*reporting and review of outcome data by individual surgeons and providers should be the norm.*

**Recommendation viii:** *The Breast Implant Registry was closed in 2005 because the majority of women registered declined to participate in follow-up research, presumably in part because of concerns about confidentiality, meaning the information generated was of low value. Yet if it is of good quality a registry system can, as other work has shown, generate valuable information to support a detailed understanding of the safety profile of medical devices over time. Sir Bruce Keogh's review should investigate the potential for re-establishing a breast implant registry in a more effective form, including an assessment of likely cost-effectiveness, and consider its applicability to other kinds of higher-risk medical device that are not currently covered by such arrangements.*

**Recommendation ix:** *The MHRA should review and further develop its communications capability to ensure they can rapidly establish and provide centralised communications regarding device alerts and related issues on an ongoing basis. This should be a proactive capability serving the needs of patients, professionals and the press / public. It should regularly and simply update interested parties around progress and current information on specific safety concerns, anticipating areas of anxiety or uncertainty and managing the information and misinformation that can circulate around safety concerns. It should also constitute a source of information for concerned individuals which is easy to access and to understand.*

**Recommendation x:** *While we found no evidence of a direct impact in this case, the MHRA Board and Department of Health should ensure that key strategic posts in the organisation do not remain unfilled for long periods of time.*

**Recommendation xi:** *The MHRA and Government should fully support efforts initiated by the European Commission to improve the operation of the regulatory system, with particular regard to higher risk devices, within the current legal framework and in advance of any specific legislative proposals the Commission brings forward. In particular, they should press for early adoption of proposals for a single European reporting portal to provide a central repository for information on device adverse incidents, accessible to all EU competent authorities. They should also press for the establishment of frequent routine teleconferences, facilitated by the Commission, to make it easier for EU competent authorities to discuss specific areas of concern regarding medical device safety and regulation on an ongoing basis, in order to improve European Co-ordination.*

**Recommendation xii:** *The MHRA and Government should endeavour to ensure that future reform of devices regulation at European level is based on a rigorous and transparent assessment of the evidence. Any implications for the work of the MHRA should be carefully costed and the Agency supported to ensure that it can discharge its functions effectively.*

**Recommendation xiii:** *The Department should ensure that a focus on continual improvement in device vigilance is an explicit component of the MHRA's annual business plan, and that arrangements are in place to monitor the delivery and impact of agreed improvements.*

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**Recommendation xiv:** *The Department of Health should ensure that the actions and lessons from the events surrounding PIP breast implants are taken into account and acted on by the MHRA. This should be assured through routine sponsorship arrangements and in the Department's Performance and Capability Review of the MHRA.*

**Recommendation xv:** *All parties - healthcare professionals, providers and patients, as well as industry - must be involved in the vigilance system as equal partners with the single aim of reducing the risk of harm to patients from medical device incidents. MHRA should therefore continuously review its activities to ensure that everything it does is consistent with this aim, and that it promotes this shared aim amongst all those involved in medical device vigilance.*

# 1. Introduction and terms of reference

## Context for the review

- 1.1. In March 2010 the French regulator Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) discovered that the manufacturer of Poly Implant Prothèse silicone breast implants had been using a grade of silicone filler that was not of the standard previously approved for implant use. The marketing, distribution and export of PIP silicone breast implants was suspended across Europe and the MHRA issued a medical device alert to all UK clinicians and cosmetic surgery providers, asking them to cease use of the implants. Subsequent toxicology tests on samples of filler material in both France and the UK suggested that there was no significant health risk to women who had already received the implants.
- 1.2. On 23 December 2011, the French Ministry of Health announced that it was advising women with PIP silicone implants to have them removed as a precautionary measure. The MHRA issued interim advice stating that, on the basis of the available evidence, women in the UK should not be advised to seek removal of PIP implants in the absence of clinical symptoms. In recognition of the anxiety of many women with PIP implants, the Department of Health (DH) subsequently announced that – where women had received a PIP implant as part of NHS treatment – they would be contacted to inform them that they have a PIP implant and to provide relevant information and advice. Women who had received PIP implants in the NHS would be offered further procedures subject to clinical need and taking full account of their wishes and concerns. The Government urged private sector cosmetic surgery providers to match the Government's offer for their own patients.
- 1.3. An Expert Group was convened under the chairmanship of the NHS Medical Director, Professor Sir Bruce Keogh, to provide further urgent advice on the safety and compassionate treatment of women with PIP silicone implants. The interim report of this group, published on 6 January 2012, endorsed both the MHRA's advice on evidence of harm and the Department of Health's subsequent policy position.
- 1.4. In the context of significant ongoing public interest in, and concern about, these events and their wider implications, the Secretary of State for Health announced on 11 January that two further reviews would be undertaken:
  - a retrospective, internal review of the actions of the MHRA and the Department of Health, led by the Parliamentary Under-secretary of State for Quality Earl Howe;
  - a forward-looking review of the regulation of cosmetic surgery, by Professor Sir Bruce Keogh's Expert Group.

1.5. This document is the report of the first of these two reviews.

## Terms of reference

1.6. The review's published terms of reference are:

“In the context of current EC directives on the regulation of medical devices and the information generally available at the time on the risks associated with breast implants, to review:

- i. what information about PIP implants was available from routine adverse reporting systems;
- ii. what external concerns about PIP implants were brought to the attention of the MHRA or the wider Department of Health, and when;
- iii. how these concerns and any related information were handled;
- iv. what advice was sought and from whom;
- v. what information was shared between MHRA and its counterparts in other countries in the EU and elsewhere;
- vi. how decisions were taken, and who was involved in this process;
- vii. what action was taken to safeguard and advise patients;
- viii. whether action was sufficiently prompt and appropriate.

The review will advise the Secretary of State on what lessons can be learned for application should similar circumstances arise in the future, and on implications for UK input to the ongoing review of the European Medical Devices Directives.”

## Methodology

1.7. The review was carried out by a small team of Department of Health civil servants, reporting directly to Earl Howe.

1.8. Initially all documentation provided by the MHRA to DH or generated by DH for briefing purposes up to the end of January 2012 was reviewed to obtain an overview of the issues and to construct a draft timeline of events from the point at which PIP silicone implants were awarded a CE mark, until 24 December 2011. Following this, wide-reaching requests were made to the MHRA and relevant colleagues in the Department

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of Health for documentation and records of discussions related to PIP silicone implants from any time up to 24 December 2011.

- 1.9. The DH library conducted a literature search for relevant published information.
- 1.10. All documents submitted were reviewed individually by the team and relevant information was recorded in a master timeline.
- 1.11. Further requests for documentation and evidence were made as necessary and as indicated by the evidence available in order to reconstruct fully the regulatory system's interactions with PIP and wider interested parties. Where documentary evidence was surmised to have existed it was requested from the relevant source or an explicit statement requested stating the document(s) were no longer available or did not exist.
- 1.12. Information was deemed relevant if it met one of the following categories:
  - communications between the MHRA or DH and PIP
  - internal MHRA or DH communications and discussions regarding PIP silicone breast implants
  - external communications regarding PIP silicone implants between MHRA or DH and
    - other EU Competent Authorities
    - the European Commission
    - clinicians
    - representatives of patients (mainly solicitors)
    - patients themselves where the communication constituted an incident report or provided evidence relevant to an incident
    - journalists and other interested parties
  - MHRA analysis of data regarding PIP implant performance
  - Ministerial submissions
  - public announcements or alerts (press notices, statements, device alerts etc.)
  - MHRA communications and discussions with subject matter experts (clinicians, toxicologists, other experts) including those on the Committee for the Safety of Devices and external experts
  - communications with professional bodies.
- 1.13. Certain information was not recorded in the timeline or considered in detail. This included:
  - general queries about breast implants

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- the contents of each individual adverse incident report regarding PIP breast implants (the review did not consider or judge the specific responses to each and every PIP-related incident report, although the team did consider a selection of incident reports to understand the process undertaken by the MHRA and the information provided by PIP).
  - documentation regarding other breast implant manufacturers.
- 1.14. All submitted documentation meeting the above criteria was further reviewed for relevance to the Terms of Reference and only included in the master timeline if it was judged to provide information useful to fulfilling the Terms of Reference.
- 1.15. Meetings were conducted with a number of MHRA personnel, either individually or in group discussions. These personnel included:
- Director of Devices
  - Clinical Director
  - Group Manager, Devices Division
  - Head of the Adverse Incident Centre
  - Head of Biosciences and Implants
  - Head of International and Parliamentary Policy
  - Freedom of Information Policy Manager
  - Biosciences and Implants Orthopaedic Team Manager
  - Senior Medical Device Specialist
  - Head of Medical Devices EU Business
  - European and Compliance Section Head.
- 1.16. Additional consultations were held with a small number of external experts including Nigel Mercer, immediate past President of BAAPS and Professor David Spiegelhalter, Winton Professor for the Public Understanding of Risk, University of Cambridge.
- 1.17. Based on a detailed analysis of the documentary and expert evidence provided, the team drafted findings and recommendations which were reviewed and commented on by MHRA and DH officials. The report was reviewed by the Chief Medical Officer for England before being agreed by Ministers for publication.
- 1.18. The review team and Earl Howe retained full editorial control of the final review, prior to its submission to the Secretary of State for Health.

## 2. Key events

**A more detailed timeline can be found at appendix 1.**

October 1997	PIP silicone gel breast implants CE marked under the supervision of TUV Rheinland.
2003 – 2007	MHRA corresponds with PIP on a number of specific adverse incident reports relating to PIP silicone implants, and begin to track trends in implant failures.
April 2007	MHRA raises concerns regarding the timeliness and quality of PIP's vigilance reporting with their notified body, TUV Rheinland, via the German device regulator. Response received in November 2007.
2007 – March 2010	MHRA continues to correspond with PIP about adverse incident report relating to silicone implants, focusing in particular on an apparent trend of relatively early rupture.
March 2010	French regulator carries out unannounced inspection of PIP manufacturing plant and discovers use of unapproved silicone filler. Recall of PIP silicone breast implants announced on 30 March and advice issued to clinicians to stop implanting them. MHRA issues Medical Device Alert to notify UK clinicians and providers. PIP goes into liquidation.
September 2010	MHRA reports that UK toxicology tests on the implant filler show no genotoxicity and no chemical toxicity.
4 October 2010	MHRA issues Medical Device Alert providing updated advice on clinical management of women implanted with PIP implants, in the light of toxicology reports.
14 April 2011	AFSSAPS publish statement with results of additional tests on implants – concludes no genotoxic effects for filler.
20 December 2011	Rumours reported in the French press that the French Government is about to recommend that women with PIP silicone implants should have them removed as a preventative measure.
23 December 2011	French Ministry of Health announces it is recommending that all women with PIP implants should have them removed. MHRA issues a press statement – not recommending routine removal of PIP silicone gel breast implants in the UK; no evidence of increase in incidents of cancer; no evidence of disproportionate rupture rates other than in France.

## 3. Regulatory context

### The regulatory framework for medical devices

- 3.1 Any account of events relating to PIP silicone implants needs to be set within the context of the EU regulatory framework for medical devices and the way it operates in the UK. This section provides a brief overview of these issues, with information on the EU medical devices regulatory system at appendix 2.
- 3.2 Medical devices are defined as all healthcare products, other than medicines, used for the diagnosis, prevention, monitoring and treatment of disease, injury or disability. Medical devices bring widespread benefits for patients and the public but no product is free of risk. Regulatory decisions therefore involve weighing risks of harm against the likelihood of benefits and determining whether the risks that exist are outweighed by the benefits that the device brings. If a product is available for use, its risks must be acceptable in relation to the potential benefits to patients and users.

### The legal framework for medical device regulation

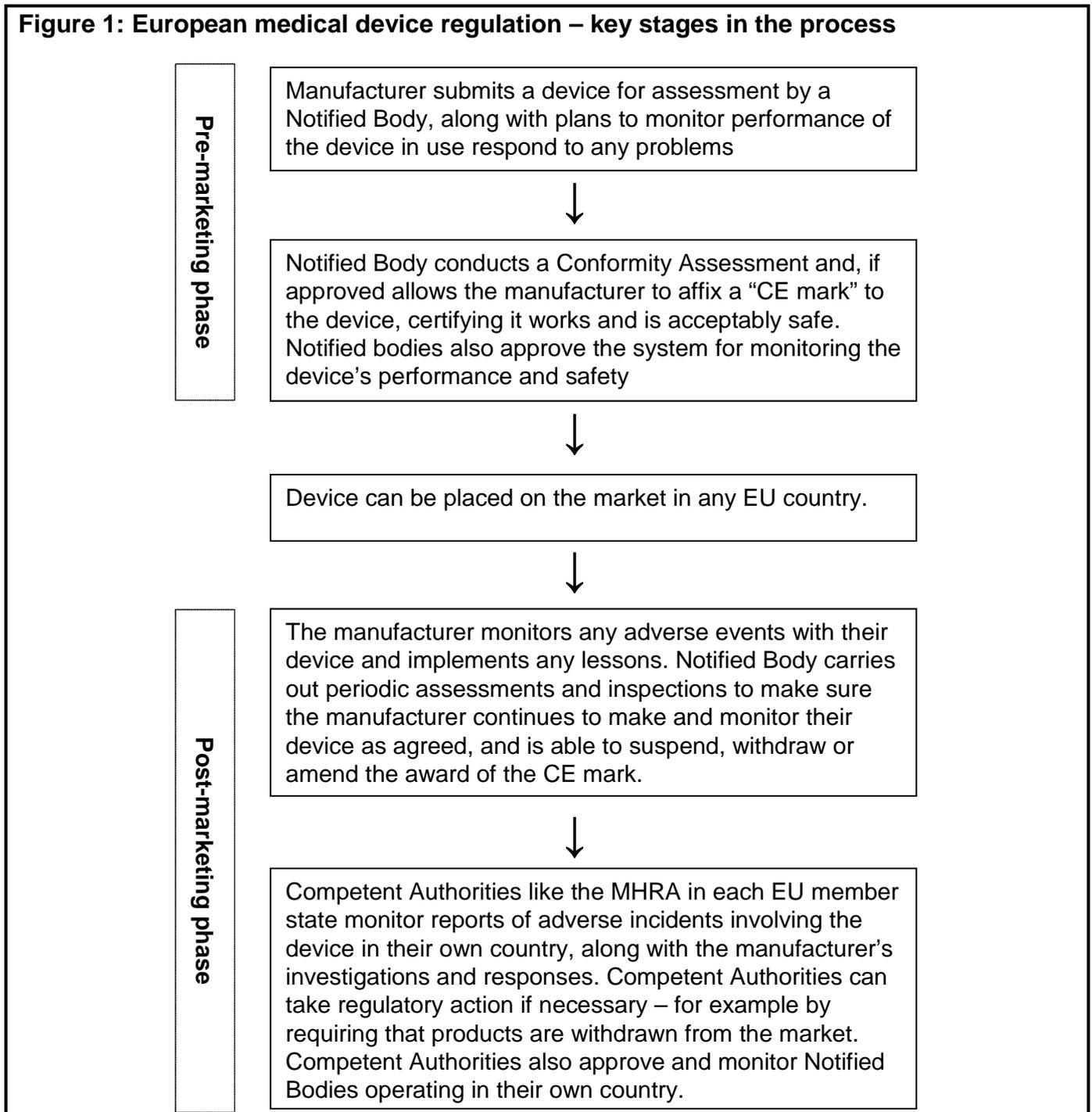
- 3.3 Medical devices are regulated under the provisions of a number of EU Directives, covering different categories of medical device. The overarching legislative framework for medical devices is part of the EU's 'New Legislative Framework', which is concerned with facilitating operation of the single market in various areas of product legislation. The principles of this Framework are common across a number of sectors; they are used, for example, in relation to the safety of toys and personal protective equipment. The relevant EU Directives are translated into Medical Device Regulations in UK law.
- 3.4 Broadly, these regulations bring into UK law EU Directives that set out:
  - how device manufacturers must ensure that the devices they manufacture are safe and fit for purpose;
  - how this is certified prior to marketing;
  - who is able to undertake certification;
  - how marketed devices should be registered;
  - how incidents involving death or serious deterioration of health related to devices must be reported by manufacturers to the competent authority (in the UK, the Medicines and Healthcare products Regulatory Agency – MHRA);
  - what the competent authority must do with that information; and

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- how the competent authority can inspect, monitor, investigate and enforce compliance with the regulations.

### Device regulation in practice

3.5 Key stages in the device regulation process are illustrated in figure 1 below.



### **(i) Pre-marketing**

- 3.6 Higher risk medical devices such as breast implants are certified by third-party private sector organisations called 'notified bodies'. There are over 80 of these independent organisations across Europe, including six in the UK. The role of notified bodies in relation to medical device regulation is to determine whether a particular medical device meets the relevant regulatory requirements and, whether, when used as intended, it works properly and is acceptably safe. This process is known as a conformity assessment.
- 3.7 If a device is assessed by the notified body as meeting the accepted standards of safety, the notified body issues a certificate of conformity which authorises use of a CE (Conformité Européenne) mark of conformity. This allows the device to be marketed in all EU countries without further controls.
- 3.8 A manufacturer can select any notified body across Europe, irrespective of location, to assess their product for a CE mark, provided that their field of expertise covers the device being considered. Once assessed and approved for market, the device can be sold in all other EU countries without further assessment by the regulatory bodies in that country (ie the marketing of a device must be allowed in the UK if a notified body in another EU country has approved the device for a CE mark). In the particular example of PIP breast implants, this conformity assessment process was undertaken by TÜV Rheinland, a German notified body.
- 3.9 For very low-risk devices, such as non-medicated bandages, the CE mark can be applied without independent assessment by a notified body on the basis of a declaration of conformity by the manufacturer.
- 3.10 The manufacturer must develop a quality system to ensure that the production and the product continue to conform to regulatory requirements. The system must include arrangements to obtain, record and review experience of the device from the marketing phase, including reviews of risk analysis and plans for any corrective action that may be required. EU guidance stipulates that this should include reviewing data on long-term effects, in particular in relation to chronic toxicity. This system must also enable the manufacturer to fulfil their obligation to notify the competent authorities of incidents related to their devices immediately on learning of them.
- 3.11 The notified body must audit the quality system to determine that it meets the necessary requirements.

### **The role of the competent authority**

- 3.12 Central to EU medical device regulation is the concept of the 'competent authority'. In the UK, the MHRA is the competent authority and has a number of responsibilities for

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the regulation of devices and promotion of medical device safety. A summary of competent authority responsibilities is included in appendix 2.

- 3.13 Competent authorities are responsible for authorising and regularly auditing the performance of notified bodies. Each competent authority is responsible for the designation and authorisation of notified bodies operating in that country. So in the case of PIP implants, TÜV Rheinland was operating as a notified body under the authority of the German competent authority.
- 3.14 In addition, if a manufacturer decides to conduct a clinical trial on his product to obtain data to support the CE marking process he must seek the approval of the relevant competent authorities before the trial can commence.

### (ii) Post-marketing

#### Post-marketing surveillance by the notified body

- 3.15 The aim of post-market surveillance by the notified body is to ensure that the manufacturer carries out the approved quality system and is providing the notified body with the agreed information. The notified body must periodically carry out appropriate inspections and assessments to make sure that the manufacturer applies the approved quality system and produces an assessment report. It may also pay unannounced visits to the manufacturer and carry out or ask for tests in order to check the quality system is working properly.
- 3.16 The notified body's periodic surveillance of the manufacturer should include checking the manufacturer's systems for reviewing experience of the device in use.
- 3.17 A notified body may suspend or withdraw a certificate, place restrictions on it or trigger an intervention from the competent authority. In such circumstances the notified body must inform the competent authority in its own country, and the competent authority must inform other competent authorities and the European Commission of such action.

#### Vigilance and incident reporting

- 3.18 The device manufacturer is central to the vigilance and incident reporting system. Manufacturers must report certain adverse incidents to the relevant national competent authority (the competent authority where the incident has occurred, unless otherwise specified) for recording and evaluation.
- 3.19 One of the roles of the competent authority is to establish a 'vigilance' programme in relation to post-market surveillance of the performance and safety of medical devices.

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- 3.20 In the UK, manufacturers must make an adverse event report to the MHRA under the Medical Devices Regulations if they become aware of 'any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or instructions for use which, directly or indirectly might lead to or have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.'
- 3.21 Manufacturers report any technical or medical reason connected with the characteristics or performance of a device which might lead to death or serious deterioration in health and that would lead to a systematic recall of devices of the same type by the manufacturer. Manufacturers are also encouraged to make reports if in doubt as to whether they fit the relevant reporting criteria and maintain systems and records for post-market surveillance.
- 3.22 Healthcare professionals and members of the public are also encouraged to report adverse events voluntarily, and the MHRA must in turn inform the manufacturer of these.
- 3.23 Where incidents are common, well documented (and identified as such in device risk assessments) and/or have been previously reported, the relevant national competent authority may agree to accept periodic summary reporting instead of individual incident reports.
- 3.24 All adverse incident reports are risk assessed by the MHRA and categorised to determine the nature of the response required. Generally the investigation into the incident is carried out by the manufacturer while the MHRA monitors progress, although the most serious investigations are led by MRHA device specialists.
- 3.25 Following these investigations, the MHRA will monitor the manufacturer response or lead on the response if appropriate. Actions can include recalling faulty products and offering warnings and advice to the health service primarily through Medical Device Alerts, but also through safety pamphlets, posters, and bulletins, and requiring the manufacturer to change designs or information. The MHRA also sends information on all reports received to the relevant manufacturer and all reports are stored in MHRA's database to assist in spotting trends that require action.
- 3.26 The MHRA has the power to prosecute when regulations have been breached. The courts can impose fines or prison sentences when the law has been broken. The MHRA can withdraw unauthorised / illegal products from the market.

### Investigations

- 3.27 The manufacturer is normally responsible for the investigation of an incident, while the relevant national competent authority (normally the one in which the incident occurred)

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monitors progress. The national competent authority may then intervene, or initiate independent investigation if appropriate.

- 3.28 The manufacturer must inform the relevant competent authority of the results of its investigation, and consult the competent authority on any necessary action. This may include the manufacturer withdrawing a product if concerns warrant it. The competent authority may take further action it deems appropriate, consulting the manufacturer where possible.

### Co-ordination and information dissemination

- 3.29 The national competent authorities are responsible for considering the dissemination and drafting of information, and communicating any corrective action needed, in their country. Where incidents of similar types occur in more than one country there may be a need for a coordinating competent authority. This should be the competent authority responsible for the manufacturer, unless otherwise agreed. The coordinating competent authority should take the lead role in discharging the competent authority functions and ensuring information is distributed to all other competent authorities involved and the European Commission.

## 4. Information on incidents and other concerns relating to PIP silicone implants

**This section considers the information available to the MHRA regarding PIP implants in the period before they were removed from sale in March 2010. It specifically focuses on the following questions from this Review's terms of reference:**

- i. what information about PIP implants was available from routine adverse reporting systems;
- ii. what external concerns about PIP implants were brought to the attention of the MHRA or the wider Department of Health, and when;
- iii. how these concerns and any related information were handled.

### Adverse incident reporting

- 4.1 Under the EC Medical Devices Directive, the MHRA as the UK competent authority is responsible for the operation of a vigilance system to record centrally and evaluate reports of incidents involving medical devices used in the UK. Manufacturers are obliged to inform the relevant competent authority of any incidents that have occurred in that competent authority's territory. Users (patients, providers and healthcare professionals) can also report incidents involving devices to the MHRA, who will pass that information on to the manufacturer. Health professionals in particular are expected to report adverse incidents under their relevant professional guidance.
- 4.2 To fulfil these obligations, the MHRA runs an Adverse Incident Tracking System, which is used to record and manage all adverse incidents reported to the MHRA. Incident reports, from users or manufacturers, are recorded and a process initiated for ensuring the manufacturer investigates the causes of an incident. The outcomes of this investigation are recorded on the system and (where appropriate) the user who reported the incident is informed of the findings.
- 4.3 Depending on the findings of the investigation, a number of actions can result, including:
  - the manufacturer modifying the device or the instructions for use;
  - addition of the incident information to 'trending' data (introduced for breast implants in 2005), which tracks the number of adverse incidents reported;

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- publicly issuing a Medical Device Alert (MDA) and using the Central Alerting System (CAS) to distribute the MDA to bring a problem with a device to the attention of relevant healthcare professionals, providers, and organisations and set out actions to avoid further incidents;
- notification of other competent authorities;
- recall of the device from the market;
- further investigation or dissemination of relevant information through other means (device bulletins, education and information tools).

### PIP silicone gel breast implant adverse incidents

4.4 The MHRA began to receive reports of adverse incidents in relation to PIP silicone gel breast implants in 2002, one of the first reports relating to a bilateral rupture of a woman's PIP cohesive silicone gel breast implants within two years of implantation. The investigation of this incident subsequently found that while one of the implants probably ruptured due to damage caused by a suture needle, the cause of the other rupture was not identifiable. The MHRA went on to receive 269 adverse incident reports relating to PIP silicone implants up to 2009 (the year before the withdrawal of PIP implants from sale following the actions of the French regulator). Table 1 demonstrates the number of PIP silicone implant adverse incidents, and implant ruptures in particular, reported to the MHRA in each year from 2001 until 2009 based on a recent analysis by the MHRA. This is not intended to represent a definitive overview of what we now know in terms of PIP rupture rates as work is still ongoing under Sir Bruce Keogh's expert group to determine the actual rupture rate for PIP implants. These data are intended to reflect the information the MHRA had available to it from adverse incident reports before 2010.

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Table 1 PIP implant adverse incident reports and sales data 2001-2009.

Year	Sales*	PIP implant adverse incident reports received by MHRA (including ruptures)	Reports of PIP implant ruptures received by MHRA
2001	4575	1	0
2002	4461	6	5
2003	6168	3	2
2004	16639	13	10
2005	12844	11	8
2006	9030	10	10
2007	9042	50	46
2008	12875	73	68
2009	8678	102	91
<b>Total number from 2001-2009</b>	<b>84312</b>	<b>269</b>	<b>240</b>

### MHRA data, personal communication, March 2012

\*PIP sales data taken from PIP DATA.doc, internal MHRA email, 7 April 2010

- 4.5 A more detailed discussion of the MHRA's analysis of PIP adverse incident trend data in comparison to other breast implant brands is provided in the section on trend analysis below (section 4.39 onwards).
- 4.6 As can be seen from the above table, the majority of PIP silicone breast implant incident reports related to rupture of implants and it is therefore understandable that much of the MHRA's attention focussed on the potential for and the reasons behind PIP silicone breast implant rupture incidents.

### Individual incident reports

- 4.7 Receipt of an incident report, whether via the manufacturer or a user, triggers the MHRA to request an investigation of the incident by the manufacturer (unless the manufacturer has already begun the investigation). This investigation must result in the manufacturer providing a final report of their investigation to the MHRA, comprising a written statement of the manufacturer's investigation and a record of any action taken as a result of the investigation.

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- 4.8 The report should include details of any relevant information obtained during the investigation, including the manufacturer's analysis of the nature of the problem reported based on their inspection of relevant manufacturing records, the returned product itself (if available) and any other relevant information. There must be a conclusion as to the root cause(s) of the incident. The report should also include, where applicable, consideration of whether there is a risk to patients or other users associated with the type of failure identified, whether the incident is isolated or indicative of a more systematic issue (and if so what the scale of the problem is and whether corrective action is needed), whether the report is relevant to any other products that the manufacturer produces and a review of the risk assessment of the device and the likelihood of recurrence.
- 4.9 This report is then reviewed by an MHRA Medical Device Specialist, who determines if the information and conclusions provided by the manufacturer are appropriate and reasonable. They can seek more information from a variety of other sources as necessary and escalate any concerns that they have, or go back to the manufacturer for more information. The Medical Device Specialist should also record the information from the incident report for wider trending and surveillance activities and then close the investigation if that is justified.
- 4.10 In the case of PIP silicone implants, having reviewed in detail a number of individual incident report files and reviewed the communications between the MHRA and PIP, the Review team believes this process was followed for all incident reports received. However, it is also clear that the investigation of incident reports by PIP was not always fully satisfactory from the MHRA's perspective. There are multiple instances of MHRA having to make repeated requests for information, clarification, or more rapid responses from PIP from 2003 onwards. In total the MHRA wrote to PIP over 20 times between 2003 and March 2010 requesting clarity or expressing some degree of concern about PIP silicone implant-related adverse incidents.
- 4.11 The first of these letters dates from 17 July 2003, when the incoming Senior Medical Device Specialist at MHRA with responsibility for breast implant adverse incident investigations wrote to PIP. Their letter highlighted that the MHRA had not received responses to the majority of questions contained in an earlier letter of 27 February 2003, many of which were originally posed to PIP in August 2002. While the majority of these incidents were not related to silicone implants (they related to hydrogel<sup>1</sup> implants, a previous PIP product voluntarily withdrawn from sale in 2000 due to a lack of safety data), ten silicone implant incidents were discussed. For at least seven of these incidents, PIP was yet to provide information requested previously. This lack of response was described to PIP as 'unacceptable' and requiring 'immediate action'. A deadline of 29 August 2003 was provided. PIP responded before the end of July to address the queries raised.

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- 4.12 Following this it is clear that PIP continued to engage with the MHRA's vigilance procedures, providing incident reports and investigations to the MHRA, who in turn asked appropriate questions and sought further information in order to clarify the incident details where necessary. Initially, the majority of incidents discussed were related to hydrogel implants (which as mentioned had already been withdrawn from sale), but over time the MHRA also sought further clarification on more and more individual silicone implant incidents reported to them by PIP and others, as well as general information on PIP silicone gel implant incidents and sales in the UK, Europe and worldwide.
- 4.13 Specifically in relation to ruptures, a number of topics were discussed with PIP through the six-year period from 2003 until the end of 2009. For example, in August 2004, following questions from the MHRA regarding implant ruptures, PIP outlined proposals to undertake electron microscopy analysis of damaged implant shells in an effort to improve the investigation of incidents involving shell failure.
- 4.14 It is notable, however, particularly from 2003 until 2007 that the MHRA needed to question the findings of a number of PIP's investigation reports. The MHRA's letters to PIP contain multiple references to anomalies in PIP incident reports. These anomalies included instances where:
- updated information on an incident contradicted information that had been provided previously;
  - PIP's investigations found that implant ruptures could have been caused by explantation, when the explantation was carried out due to the rupture having already happened; and
  - PIP's investigations referred to implants being 'totally cut' where it is not clear if the damage was caused by the surgeon or due to the implant being defective (or a combination of both) thereby failing to indicate where PIP were attributing the cause of the damage.
- 4.15 There will always be a proportion of device failures that relate to user error, and a further proportion for which the cause cannot be determined, but the level of anomalies in the incident reports that the MHRA had to query does not appear to be typical of interactions with other device manufacturers given it was specifically noted by the MHRA's relevant Medical Devices Specialist (see paragraph 4.30 below).
- 4.16 The MHRA was also in receipt of information from sources other than PIP. For example in October 2005, the MHRA wrote to a surgeon following a number of interactions regarding adverse incidents he had reported with PIP implants. The letter, from the Medical Device Specialist responsible for breast implants, highlighted two particular incidents among a wider pattern of implant failure involving 'gross tearing/disintegration of the implant shell' and, given the surgeon's involvement in the two cases mentioned

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and similar cases, asked for their comments on PIP silicone implants. It specifically asked in the cases the surgeon had seen, whether the tearing of the shell occurred in situ or if the damage was created or worsened by explantation. The letter also raised the possibility of whether the 'patch' on the shell (the section sealing the hole through which the implant is filled) could create an area of weakness on the shell, as a number of reports had indicated this was the area that tears (this was a repeated theme of correspondence between the MHRA and PIP).

- 4.17 The surgeon responded in February 2006, indicating that they could not be sure of the link between implant ruptures and the patch area, although this was possibly a feature of a number of implant types and brands. They also, however, pointed to their own less than satisfactory interactions with PIP, particularly related to a lack of explanation for the 'catastrophic disintegration' of the two implants previously discussed and an inappropriate response to a complaint letter from a patient.
- 4.18 This surgeon also offered to assist MHRA by reviewing their own data with respect to breast implants and the potential issues with patch associated ruptures, saying "it would be a feasible exercise because my series goes back a long way and it includes large numbers of implants [of different brands]...if you wish to make closer analysis of ruptured implants I would be very happy to do so but it may take sometime." There is no record of the MHRA taking this surgeon up on this offer.
- 4.19 The MHRA sought information from two other surgeons in September 2006, asking them for their views on PIP silicone implants. The Agency cited the possibility of a pattern of implant failures related to the patch area, and again asked about the possibility that 'total' rupture of the implant was present prior to explantation or if in fact there was further tearing of ruptured implants upon explantation.
- 4.20 One of these surgeons called the MHRA soon after, to report that they had suspected PIP silicone implants were rupturing more than others, but an internal review of their own data had not provided any evidence to support this. The surgeon had however stopped using PIP implants 18 months previously. They offered to provide MHRA with 'a report of my experiences' summarising their data regarding PIP silicone implants. Unfortunately, despite follow-up requests from the MHRA, in March and July 2007, no further information was forthcoming from this surgeon.
- 4.21 The other surgeon wrote to the MHRA in December 2006 stating that in their view there was a 'definite problem' with PIP silicone implants. They referred to their own experience of relatively early rupture (within 2-3 years of implantation), often located around the patch area, and also claimed to have had 'countless PIP implants break in my hand while demonstrating these implants to patients'. They too had stopped using PIP implants due to their concerns, refuted completely PIP's suggestion that implants could have been damaged by implanting surgeons or that they caused further damage during explantation, and advocated removing PIP implants from the market while further testing was undertaken.

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- 4.22 This second surgeon also offered to provide ‘any further information’ that the MHRA required. Subsequently there was further contact with this surgeon’s practice nurse in February 2007 regarding three further ruptured implants encountered since December 2006. The MHRA encouraged the nurse to report these incidents and provided the nurse with the appropriate form. There is no evidence of the MHRA requesting that the surgeon, or their practice, undertake an additional audit of their experiences with PIP implants.
- 4.23 These interactions show that the experiences of the three surgeons are not completely consistent, particularly given one’s assertion that their own data did not reveal a problem with PIP implants. It is also the case that none of the surgeons provided specific data to back-up their assertions. In one instance further information was requested by the MHRA with no success, while in the other two instances the MHRA have no record of asking the surgeons for specific or additional data on their experiences with PIP implants other than their initial responses despite offers from the surgeons. It also appears to be the case that the MHRA were approaching this issue from the perspective of trying to identify any evidence of a particular type of rupture with PIP implants (ie patch associated rupture), rather than looking specifically at whether there was a high early rupture rate.
- 4.24 We have explored with the MHRA whether greater weight could have been attached to the concerns being expressed by some individual surgeons. The MHRA pointed out that it is not unusual for clinicians to express strong views about the use of a particular device, and that they have to use all the information at their disposal to determine what further action may be appropriate. If the MHRA were to act solely on the basis of personal or anecdotal information, it could well be open to challenge by manufacturers or other stakeholders for initiating an unwarranted scare, which could damage patient and professional confidence and have serious commercial implications. In this case, the concerns expressed by individual surgeons were, however, broadly consistent with those that the MHRA was already considering, providing further justification for the MHRA to continue pursuing its concerns with PIP.
- 4.25 It is possible that if the MHRA had pursued further the interactions with the two surgeons who suggested there was a problem with PIP implants, then this may have contributed to identification of a specific problem. However, this must be considered in the context of the information the MHRA had at the time. The MHRA suspected that there was an issue with the patch area of PIP implants. They were therefore looking specifically for information in relation to patch-associated rupture and it is this that their questions to surgeons focussed on. All the surgeons provided information that was consistent with, but not conclusive about, a patch problem. Therefore the MHRA pursued the specific issue of patch-associated rupture with PIP. It is impossible to know whether, had the MHRA changed tack and asked these surgeons simply for all their data on the numbers of implant ruptures they were seeing, this would have provided the

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MHRA with additional valuable information over and above that already available from adverse incident reports.

- 4.26 The majority of the MHRA's letters to PIP, particularly up to 2007, emphasise the MHRA's focus on the potential for a specific weakness of PIP implants around the patch area. They also repeatedly questioned PIP's assertion in relation to a number of rupture incidents that the majority of shell damage may have been caused by the explantation process, and attempted to determine whether these ruptures, particularly so-called 'total ruptures', were a result of surgical error (either during implantation thus weakening the shell, or during explantation) or demonstrated a more fundamental issue with PIP implants.
- 4.27 PIP were fairly consistent in arguing that such damage could have been caused by explanting surgeons without the surgeon being aware, but the MHRA had noted that cases where PIP referred to the implant being 'totally cut' (ie the 'total' or 'catastrophic' rupture highlighted by PIP and some surgeons) tended overwhelmingly to be silicone implants (as opposed to hydrogel or saline implants), despite the fact that PIP asserted the same shell was used for all implant fillers. MHRA observed that the cut/tear in a large number of these incidents extended along the edge of the filling patch on the implant, and this led them repeatedly to pursue with PIP whether this was an inherent weakness. PIP responded repeatedly, providing details of how they too were examining the patch area and were considering and making design modifications to address any potential weakness. However, PIP did not at any point concede there was a fundamental issue; the discussions and work described were along the lines of improving designs rather than correcting a fault. Indeed at one point they cited a publication regarding silicone breast implants in general (not PIP specific) that concerned the possibility of a 'stress concentration' at the juncture of the patch and the shell, which could give rise to failure over time, indicating they did not concede this was a PIP-specific issue.
- 4.28 On a few occasions, notably in 2006, the MHRA had to chase PIP for responses to its letters. PIP also appeared to be reticent in providing the MHRA with information requested, for example in relation to electron microscopy examination of damaged implant shells, which was never provided. PIP were also relatively consistent in making the point that damage caused to the implant by the implanting surgeon without them realising was potentially the reason for the ruptures seen, which in many cases was not possible to verify either way.
- 4.29 In 2006, the MHRA began to ask PIP consistently for data on the number of reported implant ruptures, including 'total' ruptures and patch associated ruptures, and updated sales figures. It is worth noting that the current Medical Devices Directive means that it is only device manufacturers themselves that receive all available international data regarding adverse incidents related to their device. Competent authorities are reliant on manufacturers providing them with accurate and timely data regarding adverse

incidents, as they are obliged to do under the Medical Devices Directive. The MHRA was not in receipt of data related to PIP silicone implants from other countries nor was it notified of concerns with PIP's performance. It is also worth noting that the MHRA receives more device adverse incident reports each year than any other EU country with the possible exception of France<sup>ii</sup>, suggesting that they would have as good a chance to spot problems as anyone. The MHRA's use of collated PIP implant adverse incident data is discussed in more detail in the next section (paragraph 4.39 onwards).

- 4.30 Following a further delayed response from PIP and the apparent abandoning of the electron microscopy analysis, the Medical Device Specialist wrote to the MHRA section responsible for compliance complaining about PIP's delayed vigilance reporting on multiple occasions. They highlighted PIP's tendency to draw inappropriate conclusions in relation to incident investigations (ie concluding that incidents are due to 'inappropriate use' or are 'isolated incidents' when there is no evidence to support this). They also mentioned ongoing pursuit of issues with inadequate analysis of ruptured implants and 'a possible quality issue with implant shells'. They asked for advice on how to address these issues, possibly through raising them with the relevant notified body (TUV Rheinland) or the German competent authority. The MHRA compliance unit subsequently raised these concerns via the German competent authority in April 2007. TUV Rheinland committed to look into the issues during their 're-certification audit' of PIP planned for June 2007.
- 4.31 It was following this audit in 2007 that the MHRA was informed by the German competent authority that TUV Rheinland had raised the issues of late vigilance reporting and been assured that these were the result of individual mistakes. They were also assured that the staff in place at the company with responsibility for vigilance and incident investigation 'are competent'. The MHRA indicated to the German competent authority that this reassured them that the 'process is now under control'.
- 4.32 **The evidence suggests that the MHRA acted appropriately in escalating their concerns for investigation by the relevant notified body in 2007. It was quite reasonable for the MHRA to accept the assurances it subsequently received from TUV Rheinland through the German competent authority. Indeed, given the structure of the European regulatory system for medical devices, it would have been very unusual for the MHRA to question the assurances it received.**
- 4.33 While it is possible that the MHRA could have derived further helpful information had they followed up the offers made by individual surgeons, it seems unlikely that any further information would have done other than to reinforce the course of action the MHRA subsequently took in contacting the notified body about their concerns with PIP implants.
- 4.34 Following receipt of the feedback from TUV Rheinland, the MHRA continued to pursue PIP for information, with further queries on individual incidents, changes to the patch design and microscopic analysis of ruptures, chasing more information on the possible

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causes of ‘total ruptures’ and also raising the question of PIP’s expected longevity of their implants. PIP’s responses were relatively detailed but not exemplary and often resulted in more information being required. It is also clear that the MHRA began to focus more on suspicions that the longevity of PIP silicone implants may be an issue. However, whenever this was raised, PIP provided additional information supporting their case that the ruptures seen were a very small proportion of their total sales and consistent with, if not better than, other manufacturers’ models.

- 4.35 The MHRA was also aware of two published journal articles referring to specific cases of ‘total rupture’ (Lahiri 2006, Berry 2007). When these were raised with PIP they were again relatively dismissive, arguing these were not representative cases and that breast implant rupture is a recognised rare complication, as pointed out in their product information leaflets.
- 4.36 The MHRA was separately provided with a small number of independent reports on ruptured implants commissioned by an affected patient/their solicitors. One example received on 5 November 2007, concluded both implants had ruptured due to shell failure well within five years of implantation due to fatigue rather than any surgical damage or manufacturing defect.
- 4.37 In the following period, up to the end of 2009, the MHRA communicated with PIP on a number of issues related to individual incidents and investigations. Many of these were limited in scope to single investigations or a handful of incidents and were more focussed on ensuring MHRA records of incidents matched those of PIP and/or users. On one occasion, an email included a statement from a theatre manager asserting that PIP implants were getting ‘a bad reputation’ for poor longevity amongst surgeons and women, but this was potentially obscured by associated concerns with matching incident records between different parties and confusion over returning explanted implants.
- 4.38 That said, it appears that over this period, particularly in the latter half of 2009, that the MHRA became more concerned about the apparent early rupture of PIP implants as revealed by their own analysis of ‘time to rupture’ for PIP’s silicone implants.

## Trend analysis

- 4.39 In August 2005, at a meeting of the MHRA’s internal ‘Breast Implant Group’, it was proposed that the MHRA undertake a “trend review” for all breast implants. This was designed to consider the data available on adverse incidents related to breast implants in an attempt to discern any particular patterns or areas for concern.
- 4.40 The first trend review was produced on 15 November 2005 and covered all breast implant incidents from 1 November 2003 until 31 October 2005. Subsequent trend reviews were produced roughly every six months and were considered by the Breast Implant Group. In each of these reviews, from 2005 onwards, PIP silicone breast

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implants were considered along with the other major manufacturers and in each case, it was noted that there was some indication that the number of ruptures of PIP silicone implants might be higher than expected. This was generally in comparison to the numbers of ruptures seen with other brands or types of implants, using the manufacturers' sales data as a denominator.

- 4.41 It is clear that after these trend reviews commenced, the MHRA became more specific in its requests to PIP for collated data on ruptures and failures and implant sales, both for the UK and worldwide. Initially the trend reports that discussed MHRA's analysis of these data explicitly made the link with the patch issue discussed earlier as a possible cause of these ruptures. It is clear that MHRA was pursuing this with some intent, probably backed up by the data on rupture trends, which suggested there was an issue in the first place. Unfortunately, the data available to the MHRA did not provide robust evidence of an increased rupture rate for a number of reasons.
- 4.42 Firstly, even though the number of PIP silicone implant ruptures appeared higher than expected to both the MHRA and some surgeons, the actual numbers of incidents were not by any means large or conclusive. For example, the MHRA's trend review from December 2006 noted 7 PIP silicone implant incident reports (not specifically ruptures) and roughly 6250 annual unit sales. An example competitor's silicone implant was noted as having one incident report and 4870 annual unit sales. The next trend review, in May 2007, reported 20 incidents and 6250 annual sales for PIP silicone implants, while the same competitor model had three incident reports but only 1424 sales.
- 4.43 Secondly, these trend reviews did not consider the date of implantation and therefore the time taken to rupture for these implants, which is actually of more importance than simple cumulative incident report data when determining if there is a problem of implants rupturing too often. There even appears to have been some uncertainty around the accuracy of the available sales data. It is probably for these reasons that the MHRA started to focus on PIP implant longevity, as indicated by their letter to PIP in April 2007 that specifically asked for 'time to rupture' data for these implants.
- 4.44 In November 2007, the MHRA included in its trend review an analysis of PIP's time to rupture data for implant ruptures, where it was known. This is shown below. As can be seen, while there is a suggestion of an early rupture in a subset of PIP implants (the 'peak' around four years), the numbers of incidents are very small. When PIP were questioned about this analysis, they pointed out that in total, the number of UK ruptures as a proportion of total UK sales was four ruptures per 10,000 units and that it was not possible to statistically discern a trend of early rupture from such a sample (ie the pattern could be due to chance as opposed to a particular defect).

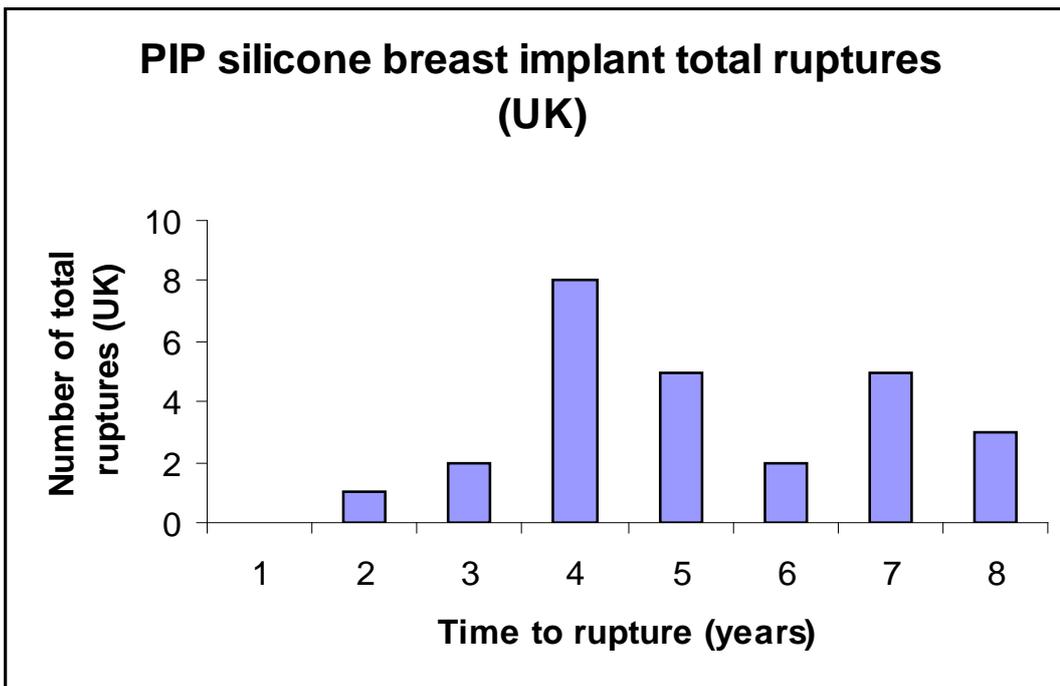
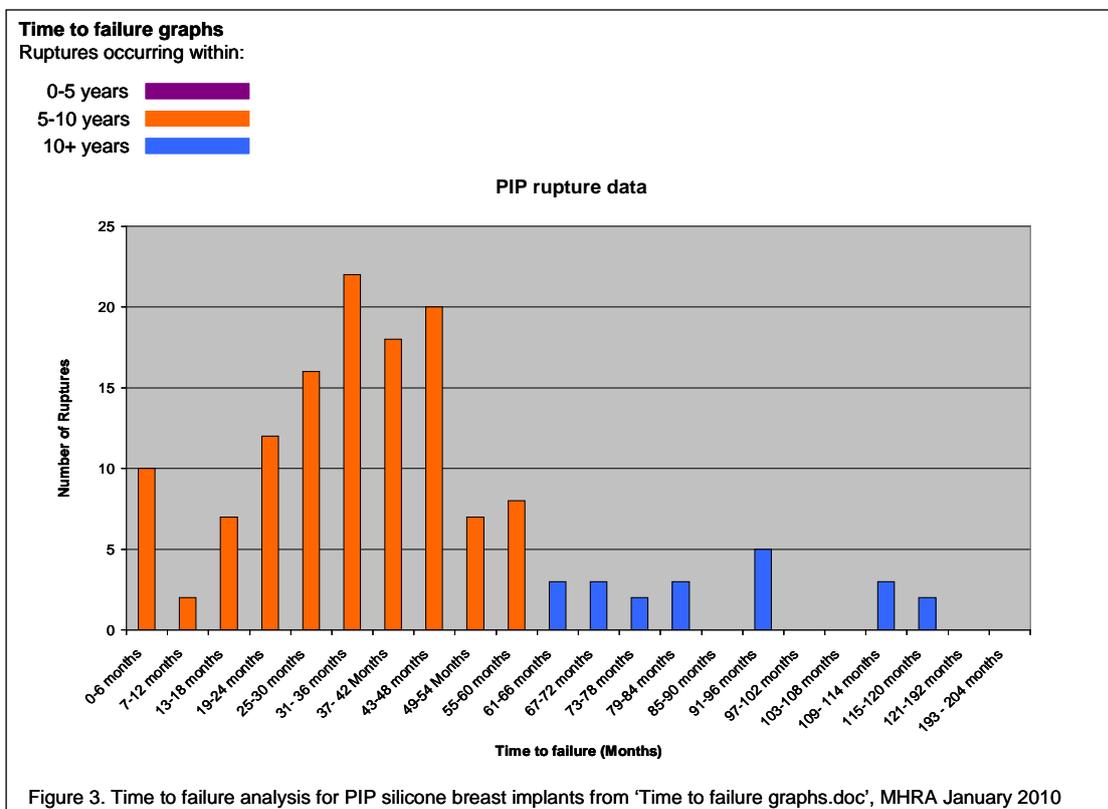


Figure 2. Time to rupture analysis for PIP silicone breast implants taken from 'BI Trend Review Nov-07.doc', MHRA November 2007.

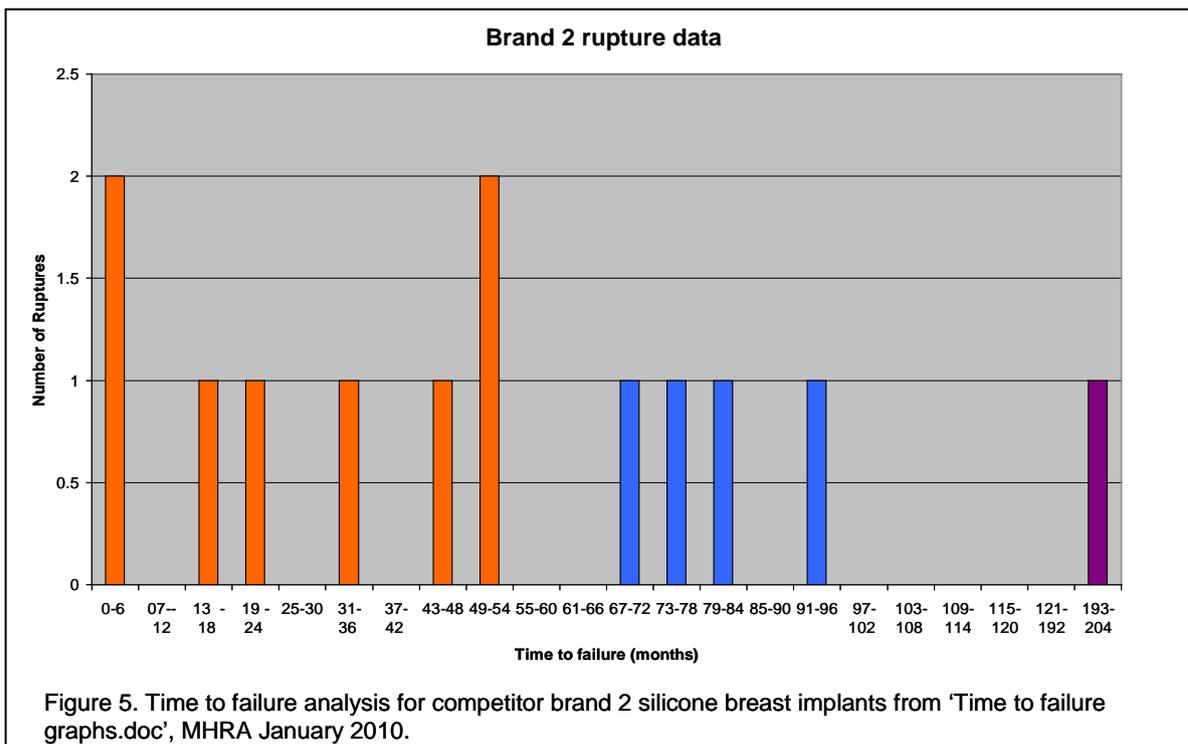
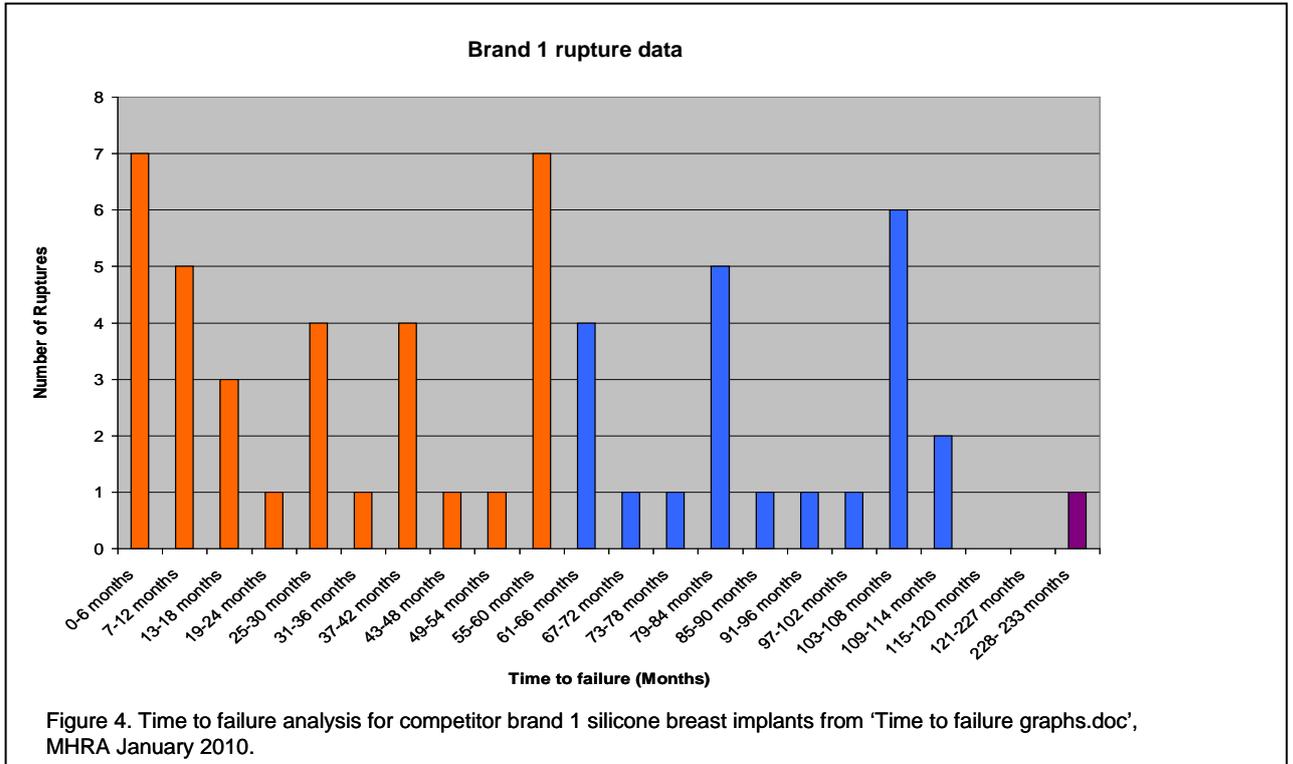
- 4.45 The MHRA did pursue this apparent pattern with PIP again in 2008, but PIP continued to refer to UK and worldwide data showing a very low number of ruptures as a proportion of sales and therefore arguing there was no evidence for a particular pattern. The MHRA's trend reviews in May and November 2008, while noting an unequal distribution of silicone implant rupture reports with apparently higher absolute numbers with PIP silicone implants, also noted PIP's own data which claimed an implant failure rate equivalent to other manufacturers and PIP's own expectations.
- 4.46 In the summer of 2009, the MHRA looked in more depth at all the information available to them and constructed another 'time to rupture' analysis. This again highlighted, with more data, an apparent early rupture phenomenon with PIP silicone implants. These data were combined with information for other implant brands and presented to the Breast Implant Group on 19 January 2010. The histograms generated are copied below (figure 3-5).
- 4.47 The conclusion the MHRA drew from this analysis was that the average (mean) time to rupture for PIP silicone implants, from the data available, was significantly shorter than with competitor brands (compare PIP time to rupture with brand 1 and 2). It was agreed at the Breast Implant Group meeting on 19 January 2010 that this issue needed to be raised with PIP and, following their response, referred to the MHRA's Committee for Safety of Devices for their opinion.
- 4.48 The MHRA's relevant Medical Device Specialist duly raised the issue demonstrated by their analysis with PIP, who responded with the information contained in figures 6-8

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below. PIP acknowledged the apparent rise in explanations over recent years, most of which were due to implant ruptures, and that this peak seemed to come around three years post implantation. They went on, however, to point to their sales figures as well. These demonstrated a rapid increase in sales from 2003 to 2004, which, they argued was mirrored by an increase in ruptures three years later due to a small proportion of the implants used rupturing. PIP stated that 'it would appear to be that there is a parallel displacement of three years between the sales curve and the explanations curve. Indeed the significant sales increase has generated a logical increase in explanations'. PIP's argument, therefore, was that as ruptures are expected in a small proportion of implants, the more implants used, the more ruptures will result, and so any peak or indication of comparatively early rupture was actually a result of the sharp increase in sales, rather than of any particular fault with the implants.



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Graph to show the UK Sales & Explantations of the IMGHC-TX breast implant as a function of time  
Number of Sales units - v - Time in years

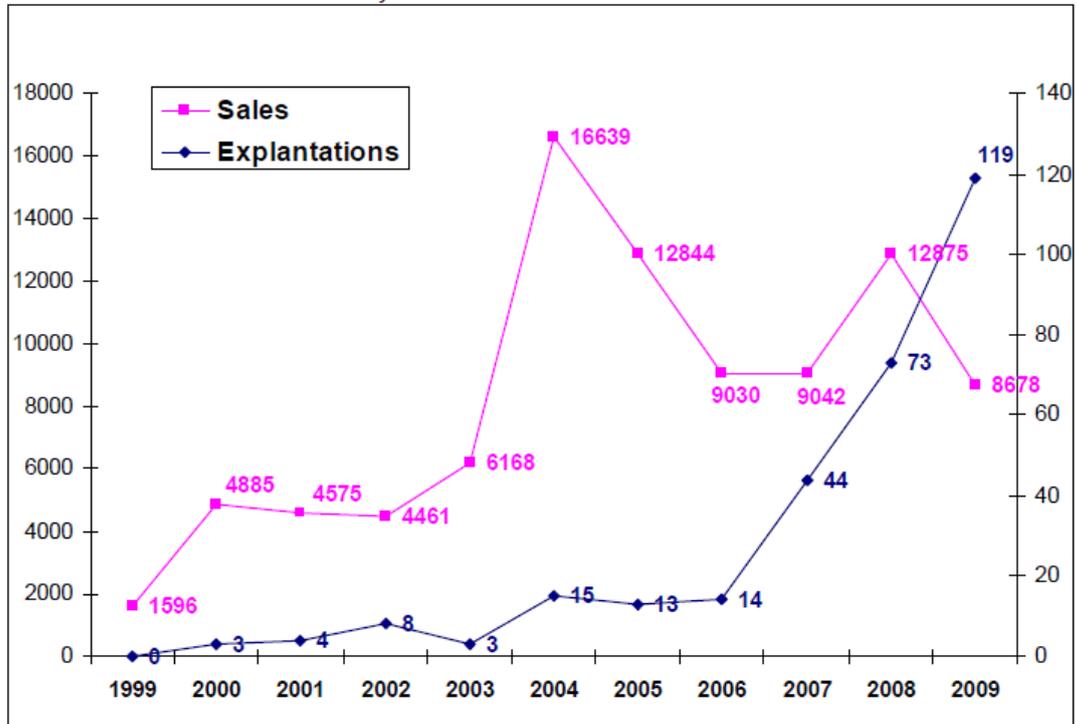


Figure 6. UK sales and explantations of PIP's IMGHC-TX model silicone breast implant over time, from PIP's own analysis contained in PIP's letter to MHRA, 25 February 2010.

Graph to show the cumulative evolution of UK Sales, Explantations & Ruptures of the IMGHC-TX breast implant as a function of time  
Cumulative Sales units - v - Time in years - v - Number of explantations/ruptures

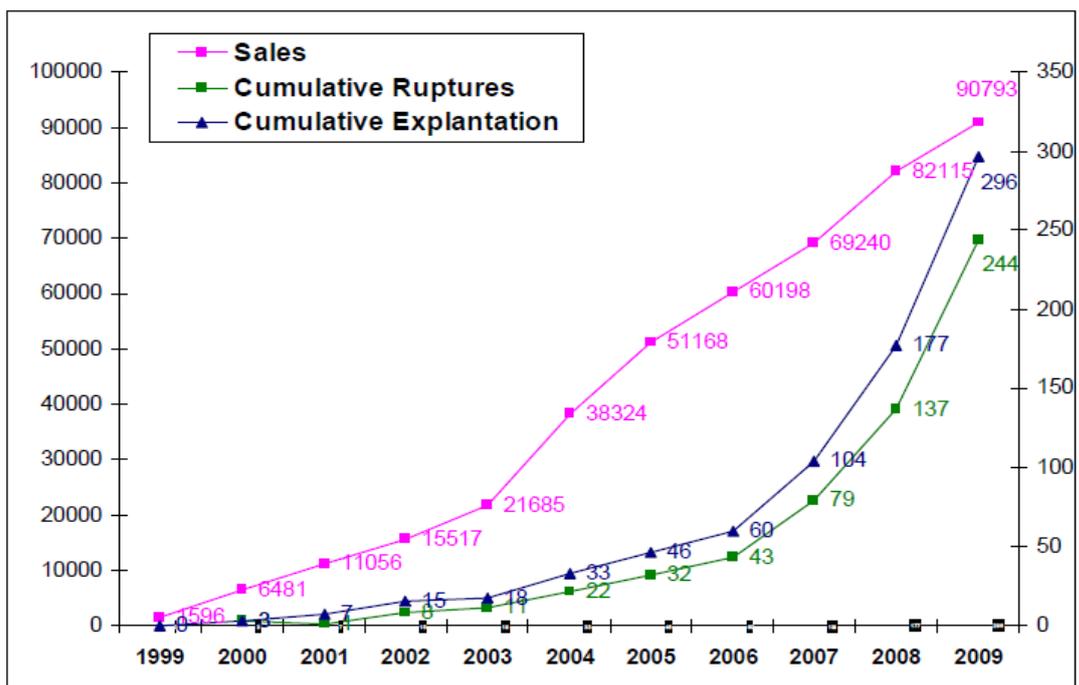


Figure 7. UK cumulative sales, cumulative ruptures and cumulative explantations of PIP's IMGHC-TX silicone breast implant over time, from PIP's own analysis contained in PIP's letter to MHRA, 25 February 2010.

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Graph to show the cumulative Explanation Rate & Rupture Rate of the IMGHC-TX breast implant as a function of the cumulative evolution of UK Sales.

Cumulative Sales units - v - Time in years - v - Rate of explanation/rupture

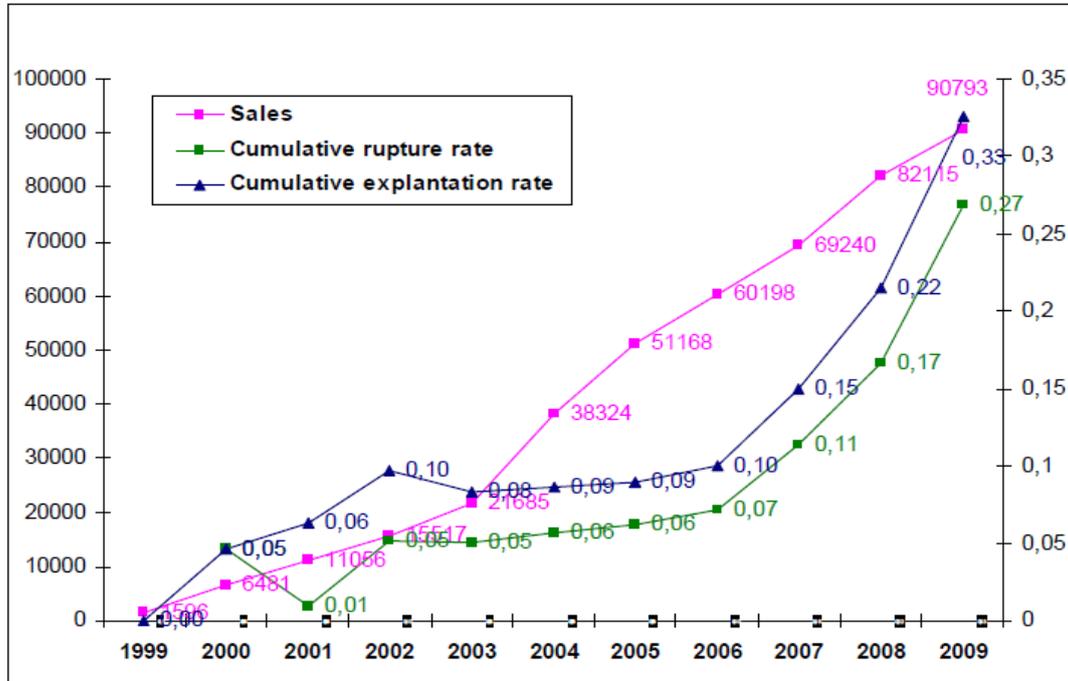


Figure 8. Cumulative UK sales and cumulative explanation and rupture rates of PIP's IMGHC-TX silicone breast implant over time, from PIP's own analysis contained in PIP's letter to MHRA, 25 February 2010.

- 4.49 The MHRA was not completely satisfied by this response, pointing to the drop in sales that occurred in 2005 and 2006 and asking why there was no corresponding drop in explanations. This query was sent on 18 March 2010. AFSSAPS suspended distribution of PIP silicone implants on 29 March 2010 and no response to this query was ever received from PIP.
- 4.50 There are a number of possible explanations for the lack of a drop in explanations following the reduction in PIP sales from 2005 and 2006. Firstly, sales data provide information on the number of discrete, individual sales over a period of time. Explanation and rupture data are related to the behaviour of implants that remain in situ once they are implanted and implants have an acknowledged increase in risk of failure with time. So, while sales may drop, the number of implants in use is cumulative (ie it keeps increasing) and it would be expected that any corresponding change in the rate of explanation or rupture would be higher the more implants that are in use, regardless of the rate at which they come into use (ie the sales data). Indeed the time lag between implant and rupture will vary between individual implants/patients, so a precise mirroring of the sales data in the rupture data would not be expected. There are appropriate statistical techniques for estimating and analysing this kind of distributed lag but they do not appear to have been considered in this instance and without them, using changes in sales volumes to predict changes in implant failure rates is not very useful.

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4.51 Secondly, PIP's reduction in sales volumes in 2005 and 2006 preceded the intervention of TUV Rheinland in PIP's internal vigilance systems. Following this intervention, the MHRA had already noted a marked increase in PIP reporting (noted in the Breast Implant Group meeting in December 2007). Therefore, it is also quite possible the increase in reports of PIP silicone implant incidents seen from 2007 onwards was, in part at least, a result of PIP's supposedly improved reporting, rather than an actual increase in failures of their implants. The MHRA noted this potential association, and observed in internal discussions that there may be under-reporting of adverse incidents for other makes of implant. This observation in itself illustrates the significant difficulties in relying on adverse incident reports to make accurate judgements about the performance of medical devices.

### Conclusions about the information available to MHRA

- 4.52 As discussed, one of the MHRA's key roles under the EU Medical Devices Directive is the operation of a vigilance system to centrally record and evaluate reports of incidents involving medical devices. **It is clear from the evidence provided to the Review team that the MHRA was indeed performing this function as laid down in the regulations. Incident reports were recorded, evaluated, followed up, clarified, challenged and used to generate overall trend data as was expected. Problems with incident reports were used to either directly require further action from PIP, or on one occasion prompted the MHRA to raise concerns with PIP's notified body, TUV Rheinland, via the German competent authority.**
- 4.53 The MHRA provided us with an overview of its current incident investigation protocol, which is designed to examine incident reports from two main angles. The first is looking at the characteristics of an individual incident or incidents in order to determine if the problem that has occurred is indicative of an issue with a device. They are looking to see if the failure that has occurred is of a nature that causes significant concern about the particular device used, a batch of devices, or indeed a type of device. In relation to this type of evaluation it is clear that MHRA was pursuing a number of possible issues with PIP silicone implants, principally the possibility that the way the patch was attached to or interacting with the implant shell was causing an inherent weakness in the implant.
- 4.54 The second aspect MHRA look at is to use pooled data from a number of device incident reports to determine if these reveal a wider trend in the type of incidents with a particular batch, type or class of devices. Again, in relation to this 'trending' analysis, MHRA was using the data available to it to try and draw conclusions about the performance of PIP silicone implants. However, it is fair to say that this type of analysis is limited by the data upon which it is based.
- 4.55 The MHRA was fundamentally dependant on the information it received from users (clinicians, providers and patients) and from PIP, both in relation to denominator data

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such as total sales and the numerator data – principally, the numbers and types of adverse incidents reported. While we have no evidence PIP was providing deliberately inaccurate or false data, concerns about other business practices PIP are alleged to have engaged in raise legitimate questions. Even assuming all the information provided to the MHRA by PIP was done so in good faith, adverse incident reporting is recognised in many fields, including healthcare, as only being able to provide a proportion of information about the actual number of adverse incidents.

- 4.56 The degree to which adverse incidents are reported is dependant on a number of factors, including recognition of the incident in the first place, and accurate, timely reporting of the incident to the relevant reporting system, either by a patient or a clinician. If, for example, a patient undergoes a ‘silent’ rupture, or the clinicians involved in resolving a rupture determine that the incident is not an adverse event (remembering for example that a certain proportion of implants are expected to rupture), then the incident may not be reported.
- 4.57 There is, in addition, a fundamental reliance on clinical engagement with the reporting system. While reporting adverse incidents is expected of clinicians, the levels of engagement vary from clinician to clinician and organisation to organisation. Studies have demonstrated, for example, that medical staff are far less likely to report adverse incidents than nursing staff (see for example Breathnach et al, 2011<sup>iii</sup>). Our investigation has also identified that on at least one occasion, a ruptured PIP implant event that was reported in a peer-reviewed journal article due to ‘huge tear’ that was evident after only 3 years in situ was not actually reported to MHRA as an adverse device incident. In this example, this was due to the surgeon not interpreting a ruptured implant as being a risk to health, and was possibly compounded by a previous interaction with the Medical Devices Agency (MHRA’s predecessor) which was not felt to be ‘satisfactory’. This demonstrates that adverse incident data is only as good as the reporting culture that it relies upon.
- 4.58 **The MHRA recognises this issue and has undertaken a number of activities to increase and improve the reporting of adverse incidents, including in relation to breast implants. But these initiatives cannot completely remove the fundamental limitations of relying on adverse incident reporting.**
- 4.59 The MHRA did not rely on adverse incident reporting alone. It also wrote to surgeons who reported incidents to seek information on whether there was a particular issue with PIP silicone implants. The information received in response was at best suggestive of a problem rather than conclusive. It seems reasonable to expect that a surgeon or provider, keeping accurate and up to date records of outcomes in their patients, including long-term follow up information, as part of good clinical governance would be able to provide regulators such as the MHRA with accurate and timely notification of an emerging problem with a device backed up by relevant data. There is no evidence in this case that MHRA was provided with such evidence by any clinician or provider prior to the French regulator halting the distribution of PIP silicone implants.

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- 4.60 The MHRA has to exercise great care in making enquiries of clinicians and professional bodies about their impressions of particular products, partly to avoid causing undue concern to patients, but also because of the impact even asking such a question can have on the market for a particular product. This makes it difficult to undertake robust investigations for evidence of failures without reasonable evidence that such problems exist. The MHRA clearly attempted to generate such evidence but were not able to do so using the information available to them.
- 4.61 A registry system has the potential to provide much higher quality data of greater utility to regulators, and to manufacturers themselves. However, while a breast implant registry was operated in the UK between 1995 and 2005, it was closed because the low level of consent from women for their details to be placed on the register made the information of poor quality for research purposes, which was the primary motivation for the registry's creation. This issue would need to be addressed in any future efforts to re-establish a registry for breast implants and / or other high-risk medical devices.
- 4.62 **It should be noted that all the information in the MHRA's possession suggested that if there was any problem with PIP silicone breast implants then it was possibly an issue with PIP implants rupturing more often and sooner than expected. At no point throughout the period from 2002 until 2010 when they were receiving reports of incidents with PIP implants, was there any suggestion that the implants contained a filler material other than that which had been approved by the German notified body. The fact that there is still a lack of conclusive evidence that PIP implants were rupturing at a greater rate than other implant types, demonstrates the difficulty faced by the MHRA (or any similar body) in detecting any issues with PIP implants through their post-market vigilance activities.**
- 4.63 The task of assessing device failure in breast implants is more complex than that associated with devices which should "never fail". Rupture was and is a well-known risk associated with all kinds of breast implant, and a proportion of implants would be expected to rupture during their implanted life. This introduces further complexity into the task of analysis.
- 4.64 The review team did not find any evidence of the MHRA ignoring, missing or disregarding conclusive evidence of problems with PIP implants. What we have observed is a regulator having to undertake repeated and extensive correspondence with a manufacturer over a significant period of time, in an effort to determine if there is an issue with a device or if all the adverse incidents seen are as expected given a recognised (but small) risk of device failure. We have been struck by the volume of this correspondence (over 20 individual letters from the MHRA to PIP between 2003 and 2010 some covering up to 20 pages, plus additional interactions via email) and the obvious concerns that the MHRA did have at times with PIP's behaviour. In hindsight, knowing what we now know about the practices at PIP, this body of evidence could be seen as suggestive of a problematic manufacturer. There is no way to know if a similar exercise to this Ministerial Review, but conducted prior to March 2010, would have

suggested similar concerns. But we do think there is merit in exploring how the MHRA could undertake periodic reviews of its interactions with manufacturers to determine if seemingly low-level issues, such as those associated with accuracy and timeliness of reports, coupled with ongoing but not severe concerns about incident trends and anecdotal reports from clinicians, solicitors and patients, could be indicative of more fundamental concerns.

- 4.65 It is important to note that any regulatory system is the backstop to underpin safety in health care. No regulator can provide an absolute safeguard, particularly in the event that deliberate and potentially criminal efforts are made to subvert it. Rapid identification of and intervention in patient safety issues is first and foremost the responsibility of frontline clinicians, provider organisations and their leaders. We have heard that there remains scope to improve professional awareness of and participation in arrangements for reporting adverse incidents. The MHRA has a key role in this but it must be actively supported by professional bodies, provider organisations and others with a stake in the system.

## Recommendations

**Recommendation i:** *There is a system-wide responsibility for maximising reporting of adverse device incidents and for ensuring that reports are of high quality. The MHRA should continue to work with health providers (both NHS and private), professional bodies, regulators and patient groups to promote the best possible understanding of the role of the reporting system and to ensure that professionals in particular understand what they have a duty to report – and why.*

**Recommendation ii:** *The MHRA should work with partners to explore the potential for strengthening the network of Medical Device Liaison Officers, and emphasising the importance of the role within health care providers. In particular, it should work with the main private health care providers to encourage the establishment of a network of Medical Device Liaison Officers in that sector to complement that which exists in the NHS.*

**Recommendation iii:** *The MHRA should press ahead with planned work to improve its periodic trend analysis of data on adverse device events, including a more systematic focus on analysis of the rate of reported incidents relative to sales. This work should incorporate provision for periodic expert, external statistical input to support analysis of the available data on adverse device events and help identify what other data are needed. It should include consideration of how best to use additional sources of information alongside incident reporting to assist in the early identification of issues.*

**Recommendation iv:** *While acknowledging that a “one size fits all” approach to consideration of cumulative vigilance information will never be appropriate given the wide diversity of medical devices on the market, the MHRA should ensure that it has clear operating procedures for the*

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*periodic review of ongoing series/categories/types of device incident reports, particularly for higher risk products, including appropriate involvement of external experts. Plans to involve members of the Committee on Safety of Devices in such activity should be implemented without delay.*

**Recommendation v:** *The MHRA should review the way in which it manages records and knowledge on ongoing device issues so that they can be retrieved and analysed more easily for the purposes of retrospective review and learning, and the construction of narrative information to support the periodic review procedures mentioned above.*

**Recommendation vi:** *The MHRA should review the processes and governance it uses to ensure that timely and appropriate action is taken in pursuing responses from manufacturers, notified bodies or others, and in ensuring appropriate regulatory actions take place in a timely manner.*

**Recommendation vii:** *Sir Bruce Keogh's review should examine ways of promoting a stronger culture of clinical governance, clinical audit and reporting in cosmetic surgery. Routine incident reporting and review of outcome data by individual surgeons and providers should be the norm.*

**Recommendation viii:** *The Breast Implant Registry was closed in 2005 because the majority of women registered declined to participate in follow-up research, presumably in part because of concerns about confidentiality, meaning the information generated was of low value. Yet if it is of good quality a registry system can, as other work has shown, generate valuable information to support a detailed understanding of the safety profile of medical devices over time. Sir Bruce Keogh's review should investigate the potential for re-establishing a breast implant registry in a more effective form, including an assessment of likely cost-effectiveness, and consider its applicability to other kinds of higher-risk medical device that are not currently covered by such arrangements.*

## 5. MHRA action and advice

**This section primarily considers the decisions and actions that the MHRA and the Department of Health took following the AFSAPPS recall of PIP silicone breast implants in March 2010 through to 24 December 2011. Decision-making and action relating to information available to the MHRA prior to March 2010 is considered in the preceding sections. It specifically focuses on the following questions from this Review's terms of reference:**

- iv. what advice was sought and from whom;
- v. what information was shared between MHRA and its counterparts in other countries in the EU and elsewhere;
- vi. how decisions were taken, and who was involved in this process;
- vii. what action was taken to safeguard and advise patients;
- viii. whether action was sufficiently prompt and appropriate.

### Immediate response to the French regulatory action of March 2010

- 5.1 On 29 March 2010, the French competent authority AFSAPPS announced that it was recalling all PIP silicone breast implants, citing the results of its recent inspection of the PIP manufacturing facility and concerns over the potential use of unapproved implant fillings. The MHRA contacted AFSAPPS for more information the following day, and began to plan its response to the French action.
- 5.2 Staff in the MHRA Biosciences and Implants Unit and Devices Clinical team immediately identified the need to issue a Medical Device Alert (MDA) to ensure that clinicians stopped using PIP implants, and to contact the UK distributor to ensure that any stock was quarantined. A decision was made that the usual 24 hour consultation prior to issuing an MDA would be foregone, to ensure that the alert could be issued before the forthcoming Easter weekend. The MHRA contacted Cloverleaf, the UK distributor of PIP implants, on 30 March confirming that implantation of PIP implants should cease and instructing them to remove the product from potential use. The MHRA also alerted BAPRAS to the action being taken. The clinical advice to be offered was discussed with the Committee on the Safety of Devices (CSD) plastic surgery specialist, Professor Simon Kay.
- 5.3 On 31 March 2010, the MHRA issued Medical Device Alert MDA/2010/25, instructing users to cease implantation and return unused devices to the UK distributor. A

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submission was made to DH Ministers, copied to officials in the other UK Health Departments, informing them of the situation and the action being taken. The submission was made in the pre-election period, and was for information not decision; there is no record of a response.

- 5.4 The MHRA issued a press notice to accompany its Alert, and contacted relevant professional bodies (including BAPRAS and BAAPS) to update them on the action being taken. Communications with professional bodies emphasised that it was not clear at present whether the unauthorised filler material was toxic. The MHRA press notice stated that the French regulator was undertaking tests on the unapproved gel filling to establish the level of risk to women, and promised further advice when information became available.
- 5.5 The MHRA was in regular contact with AFSSAPS from 30 March onwards. Initial contact focused on seeking more information from the French on what they had found, securing details of the proposed plans for implant testing, sharing recent MHRA exchanges with PIP on device performance and offering access to devices explanted from women in the UK. The MHRA Chief Executive was in personal communication with AFSSAPS on 31 March to seek information on the French findings, and also signed off the submission the Agency sent to Ministers informing them of the situation.
- 5.6 The MHRA did not advise clinicians to contact women with PIP implants, on the basis that until toxicology information was available there was no advice to offer on the need for intervention, over and above the clinical investigation that would normally be undertaken if a woman reported symptoms of an implant rupture. Communications between the MHRA and professional bodies show a legitimate concern to avoid causing unwarranted panic. The advice the MHRA issued was based on a reasoned assessment of the evidence and appears to have been consistent with a broad clinical consensus on the action that could reasonably be recommended. Consistent advice was given by the MHRA and the professional bodies.
- 5.7 The French regulator was clear that, while an unapproved filler had been used, further testing was required to determine whether this presented a risk to women. Similarly, there was no robust evidence provided to demonstrate an increased risk of implant rupture.
- 5.8 Had the MHRA had evidence of a risk to women from the filler it would very likely have taken a different approach – for example it worked with the manufacturer of Trilucent implants some years earlier to co-ordinate an active removal programme on the basis of evidence suggesting a toxicity risk from the soya-based filler used in those devices. In the case of PIP implants it appears to have determined there was no immediate benefit in asking clinicians to contact implanted women in March 2010, before information on toxicity was available, as clinicians would have been able to provide no useful information to patients.

- 5.9 **Under the circumstances, the MHRA responded promptly and appropriately to the French regulatory action at the end of March 2010, to ensure that women in the UK were protected from the new implantation of PIP devices from that point forward.**

### Advice on toxicology

- 5.10 AFSSAPS indicated at the end of March 2010 that it planned to undertake rigorous testing of PIP silicone implants, to establish both any toxicology risk from the unapproved filler and any structural problems with the shell. As the competent authority with lead responsibility for vigilance on PIP products, it was appropriate for AFSSAPS to take this lead in ensuring that appropriate follow-up testing was carried out.
- 5.11 AFSSAPS initially advised that the results of its toxicology tests should be available in a matter of weeks (though structural tests were expected to take longer). The MHRA's Clinical Director for Devices sought expert advice from Professor Ian Kimber, a CSD member and Professor of Toxicology at the University of Manchester, on the appropriateness of the tests the French regulator planned to carry out and was reassured that the planned tests were indeed appropriate. It appears entirely reasonable that the MHRA did not at this stage decide to commission its own testing of PIP implants, though it prudently secured a stock from the UK distributor in case these were subsequently required.
- 5.12 In the event, the French toxicology testing was subject to repeated delays. The MHRA sought updates on progress in May 2010, and again in June. AFSSAPS reported that there were delays associated with legal proceedings, and the anticipated date for receipt of results slipped to the end of July for toxicology and the end of August for genotoxicity. Towards the end of June, the MHRA's Chief Executive became aware through a chance conversation with the French regulator that the French courts had impounded local stocks of PIP implants, that this had delayed work on testing and that work would not be complete before mid September. This was communicated to competent authorities by AFSSAPS at a Vigilance MDEG meeting on 30 June. MHRA officials concluded that, in view of ongoing delays and a lack of confidence in the dates now being suggested for the availability of the French testing results, MHRA should consider commissioning its own toxicity testing on the implant filler.
- 5.13 On 6 July 2010, following consultation with Professor Kimber, and with independent genotoxicity expert Professor David Kirkland, the MHRA commissioned an accredited external laboratory to undertake UK toxicology testing of PIP implants. These tests were more limited in scope than the French testing plans, but were designed to give quicker results. Commissioning was undertaken very rapidly, within a few days of the decision to pursue independent UK testing. The MHRA subsequently wrote to AFSSAPS complaining of a lack of information about delays to testing, and setting out its own

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testing plans. AFFSAPS e-mailed all European competent authorities at the end of July asking if they had commissioned testing and, if so, to share the results when available. MHRA officials noted at the time that the interactions with AFSSAPS highlighted a need for improved networking arrangements among the European competent authorities.

- 5.14 The MHRA decided not to commission separate structural testing of PIP implants. This appears reasonable given the clear focus of public and professionals on toxicology issues, the ongoing French structural testing and the longer lead times associated with structural tests.
- 5.15 There was also an interaction with the wider Department of Health at this point, in an attempt to quantify the implications for the NHS should toxicology testing suggest a need for women with PIP implants to have them removed.
- 5.16 The MHRA began to receive the first batch of early toxicology test results in late July. An update was provided to DH Ministers on 19 August, and information was shared informally with the British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS) and the Association of Breast Surgery (ABS), to support the development of communications for health professionals when the final results were available. The MHRA issued a statement on 26 August 2010 saying that it had received preliminary results of UK toxicology testing, was analysing the results and would issue further advice to clinicians and implanted women once the results were known. At this time MHRA was also triangulating its own test results with preliminary findings that were beginning to be shared, in confidence, from French testing.
- 5.17 Discussions with external advisers and with CSD members in late August (20 – 28 August) supported the conclusion that the UK test results showed no evidence of safety risks associated with the unauthorised filler materials. Ministers were informed on 1 September 2010 and agreed a recommendation that the results should be published quickly. The MHRA published its testing results on 3 September, stating that they showed no genotoxicity (cancer risk) or chemical toxicity and linking to advice on clinical management from the ABS and BAPRAS.
- 5.18 AFSSAPS published the results of its testing on 28 September 2010. The tests found no evidence of genotoxicity or chemical toxicity (though one genotoxicity test was inconclusive and further testing was underway). Mechanical testing suggested that there may be an increased risk of rupture, though this was contradicted by the results of Australian testing shared with the MHRA which concluded that the implant shells met required standards “by a fair margin”. The French tests also suggested that the gel could act as an irritant. The MHRA considered the results in correspondence with external expert clinical advisers, along with information from Australian testing, and concluded that they did not justify a change of existing advice against routine scanning or preventative removal.

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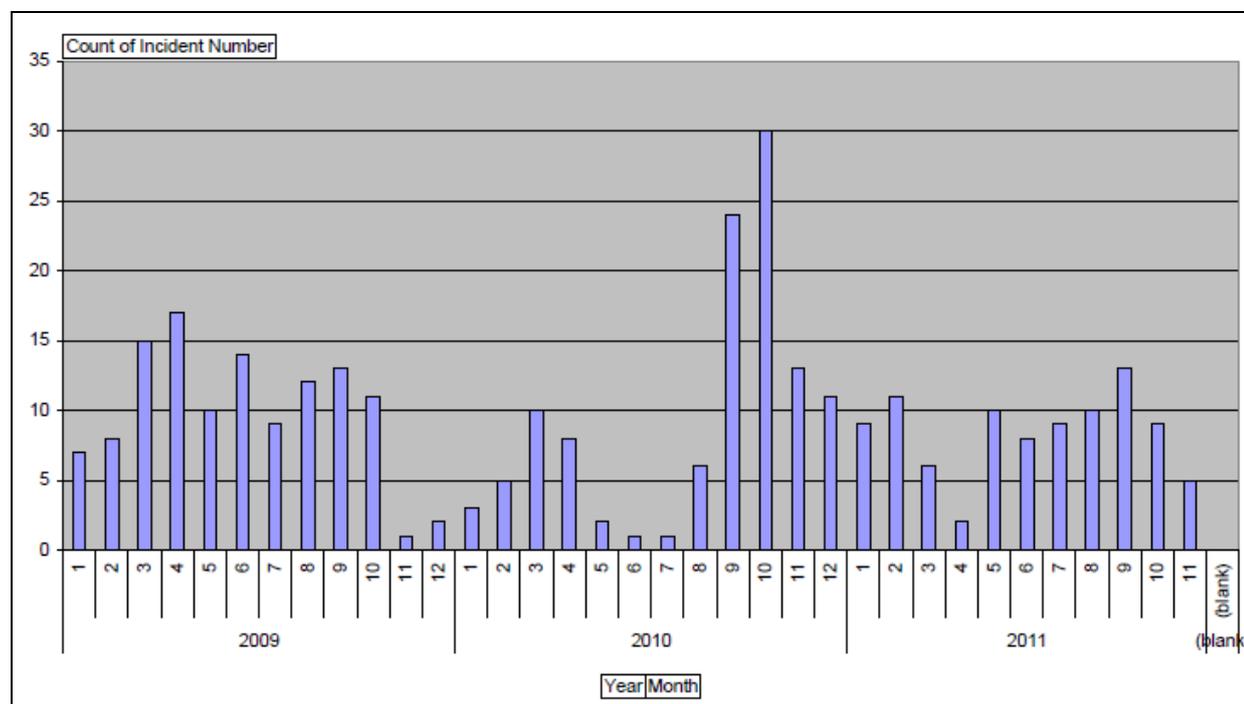
- 5.19 The MHRA published a summary of the French test results on its website on 28 September, stating that further advice was being taken from UK clinical and toxicology experts and that if women had concerns they should speak to their implanting surgeon. AFSSAPS completed its genotoxic testing in 2011 and published the final results on 14 April. The MHRA issued a press statement on 21 April 2011 reporting the French regulator's conclusion that their tests showed no evidence of genotoxicity or chemical toxicity in the filler of PIP silicone breast implants.
- 5.20 **Implanted women and their clinicians would very understandably have welcomed earlier advice on the potential toxicity risk associated with PIP silicone implants, and this advice should have been available in early summer 2010 had French testing work proceeded as initially planned. Once it became clear that the French tests would be significantly delayed, the MHRA acted very promptly in commissioning independent UK testing and this helped to provide reassurance to women several weeks before the initial French testing results were available (and some months before final French testing results were published).**

### Continued monitoring of adverse incident reports

- 5.21 The withdrawal of a medical device from the market does not affect the responsibility of clinicians and providers for reporting adverse incidents associated with its use, or the responsibility of competent authorities to record and monitor those incident reports. In the case of PIP silicone implants, the MHRA continued to monitor adverse incidents reported in the UK. The number of reported adverse events rose in 2010 - perhaps as the result of an understandable increase in reports around the time the results of toxicology testing attracted publicity in the autumn of 2010, but the number of reported ruptures and overall incidents actually fell in 2011 (see figure 9 and table 2).

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Figure 9: Monthly number of adverse incident reports for PIP breast implants reported to the MHRA from January 2009 to 25 November 2011.



From 'PIP sur 25 Nov 2011.pdf', internal MHRA email, 25 November 2011

Table 2: PIP implant adverse incidents and sales data 2009-2011\*.

Year	Sales	PIP implant adverse incident reports received by MHRA (including ruptures)	Reports of rupture received by MHRA
2009	8678	100	95
2010	Unknown	166	140
2011	0	103	78
<b>Total</b>	<b>8678</b>	<b>369</b>	<b>313</b>

Adapted from 'PIP DATA to December 2011 – Amended.doc', internal MHRA email, 22 December 2011.

\*The number of adverse incidents shown in table 2 may be higher than the number of adverse incident reports received shown in figure 9 because some adverse incident reports provide details for more than one event.

5.22 The Device Alert issued in March 2010, and subsequent wider publicity, would be expected to lead to clinicians paying closer attention to any problems their patients experienced with PIP implants, thus potentially increasing the likelihood that adverse incidents with these implants would be reported. This appears to have happened in 2010 as demonstrated in the above data. There may also be countervailing factors,

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potentially including a misperception among some clinicians that it was not important to report adverse incidents for a device that had been withdrawn. However, the fact is that the reported data, which MHRA continued to monitor, did not appear to show a significant increasing failure rate for PIP silicone implants in 2010 and 2011, other than a peak in the autumn of 2010.

- 5.23 The closure of the manufacturer in March 2010 left a gap in the operation of vigilance arrangements because, as we have observed, the manufacturer was the point at which information on all reported adverse incidents was brought together. EU guidance on implementation of the Medical Devices Directives does provide for a competent authority to take a lead in co-ordinating adverse event data on product on a Europe-wide basis. Where such work is undertaken, the guidance suggests that it is led by the competent authority for the member state in which the manufacturer is based, also known as the co-ordinating competent authority – which for PIP was AFSSAPS.
- 5.24 European Competent Authorities, including the MHRA, compared their information on rupture rates for PIP implants in December 2011 (see paragraph 5.34 below) and AFSSAPS requested information on UK ruptures from MHRA. But prior to that there does not appear to have been any attempt to collate information on implant ruptures at a European level. It is also worth noting that even when data were compared in December 2011 they were not felt at that time to be suggestive of an unexpectedly high rupture rate, with the exception of data from France.
- 5.25 **The MHRA discharged its responsibility for continued monitoring of UK adverse incident reports on PIP silicone implants after March 2010. The primary focus of efforts in the UK and internationally was – quite rightly – on the filler and on establishing any potential toxicity. Information on potential rupture risk was mixed, with French testing showing a potential increased rupture risk but Australian testing conflicting with this conclusion. There is no good evidence to suggest that the MHRA should have taken additional investigative action between March 2010 and December 2011. However, with hindsight greater effort could have been made to co-ordinate the activities of, and share information among, competent authorities in continuing to monitor adverse events associated with PIP silicone implants after March 2010. We make recommendations on the scope for better co-ordination of EU activity on device vigilance in section 6 of this report.**

## Cancer risk

- 5.26 While the potential for genotoxicity was addressed in UK and French testing conducted in 2010, there was a renewed focus on this issue in January 2011 when the US Food and Drug Administration (FDA) issued a safety communication on reports of Anaplastic Large Cell Lymphoma (a very rare cancer) in women with breast implants. The FDA report advised that women with breast implants may have an increased (but still very

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small) risk of developing this cancer. Although this report made no mention of PIP silicone implants (and indeed they were not marketed in the USA) a reported case of ALCL in a French woman has been linked to the French Government's recommendation on preventative removal of PIP implants in December 2011.

- 5.27 The MHRA considered the FDA report internally and took expert advice from the British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS), the Association of Breast Surgeons (ABS), the British Association of Surgical Oncologists and the National Clinical Director for Imaging, Dr Erika Denton, before issuing a Medical Device Alert on 16 February 2011. The Alert highlighted the uncertain evidence from the FDA, and indicated that no change to current best practice was indicated. Surgeons were encouraged to report adverse events, and women to self-examine and seek medical advice if they were concerned. This was not significantly different to the advice issued by the FDA. At that time the MHRA had received no reports of women with any type of breast implants in the UK having a diagnosis of ALCL, and previous work with relevant professional bodies and cancer registries had concluded that there was no evidence to indicate an association between breast implants and cancer.
- 5.28 **Taken alongside the results of UK and French toxicology testing, there appears to have been no reason for the MHRA to issue different advice on the implications of the FDA study for women with PIP silicone implants.**

## Breast feeding

- 5.29 The results of French toxicology tests published at the end of September 2010 indicated the possibility of silicone 'leaching' through the shell of PIP implants. As a result, in October 2010 the MHRA sought advice from a toxicology expert on the potential risks of PIP silicone breast implants in relation to breast feeding. In December a meeting was arranged with experts from the University College London Institute of Child Health, which took place in early February 2011. As a result of this meeting a literature review was undertaken to assess the available evidence on the potential risk of breast feeding and silicone implants. This review was completed by the MHRA within two weeks of the meeting and concluded that there was "no current evidence to suggest that silicone or any derivatives are passed to the infant through the breast milk". This information was included in an update to the breast implant pages of the MHRA website in March 2011. **MHRA appear to have acted appropriately in evaluating and publicising the evidence about silicone breast implants and breast feeding.**

## PIP implants manufactured before 2001

- 5.30 The information published by AFSSAPS following their inspection of PIP in March 2010 indicated that an unauthorised filler material had been used by PIP in implants marketed from 2001 onwards. The MHRA subsequently received around 14 enquiries from

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women who had received PIP implants prior to 2001, asking if their implants were affected, and replied to them on the basis of the French advice, ie that they were not affected. In January 2012, prompted by continued enquiries from women with PIP implants, the MHRA sought further information from AFSSAPS about the filler used between 1997, when the implants were first granted a CE marking, and 2001. AFSSAPS confirmed at that stage that they did not have definitive information on the filling used before January 2001. Following further communication between the MHRA, the UK distributor of PIP implants, AFSSAPS and the German notified body, AFSSAPS contacted all EU competent authorities on 12 March 2012 to inform them that to date, there was no guarantee that PIP breast implants manufactured prior to 2001 contained the approved filler. This did not result in a change to the advice issued by the MHRA and DH, but meant that the issue affected up to 7000 more women in the UK than initially thought and led to efforts to ensure that those women were informed of the position.

- 5.31 The MHRA, along with regulators in other countries, acted on the basis of information provided by the French authorities in developing its advice for health professionals and affected women. It was not until the MHRA pressed for more details, following public enquiries, that AFSSAPS issued further information to competent authorities about the uncertain evidence on implants manufactured prior to 2001. **While it might be tempting to suggest that the MHRA could have pursued the issue with AFSSAPS at an earlier stage, the French regulator had issued clear information focusing on implants manufactured after a specific date and it was reasonable for the MHRA to believe at the time that the information provided was accurate. This issue does, however, further illustrate the case for improvements in the way information is exchanged between competent authorities.**

### French policy change in December 2011

- 5.32 On 24 November 2011, AFSSAPS informed other competent authorities of press reports regarding the death in France of a woman with PIP implants who had developed lymphoma. The MHRA reviewed available evidence, including its own adverse incident data and reaffirmed that there was insufficient evidence to indicate any association with cancer. In view of this, no change to existing advice was judged necessary. Following enquiries from a private clinic, MHRA officials considered putting a position statement on its website. After consideration they decided not to at that stage because of a concern that this might create a false impression of significance, leading the public to conclude there was a link. The MHRA remained in contact with AFSSAPS during December, seeking more information on the French lymphoma case.
- 5.33 On 20 December 2011, reports appeared in the French press suggesting that the French Director General of Health (in the French Government, not AFSSAPS) was stating that all women with PIP implants should have them removed. The MHRA

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contacted AFSSAPS, who replied that no decision on routine explantation had been taken and this was being clarified with the French media. On the same day, AFSSAPS contacted European competent authorities to say that the French government would decide on 23 December whether they would be recommending the explantation of PIP implants from French women. The MHRA press office notified DH Ministers' offices of the press interest.

- 5.34 On 21 December MHRA officials took part in a telephone conference, chaired by the European Commission, with 10 other EU countries to discuss the AFSSAPS communication. All participants agreed that there was no evidence of increased incidence of cancer associated with PIP implants, and no evidence of disproportionate rupture rates other than in figures cited for France. Information from the Australian competent authority was consistent with rupture figures reported from other countries with the exception of France. A further update was given by email to DH Ministers' offices and other UK Health Departments, and the MHRA issued a press statement saying that AFSSAPS had not yet confirmed what advice it would be giving in relation to the need to remove PIP implants. This statement was also drawn to the attention of the relevant professional bodies. The MHRA undertook to look at the French safety statement and supporting evidence carefully when it was issued as a matter of priority and issue further advice as necessary.
- 5.35 Also on 21 December, the MHRA took steps to establish an expert advisory group to consider information and evidence to date, including any new information presented by the French authorities, and contacted several leading experts to invite them to join the group. Direct contact was also made with major private sector providers to share the lines the MHRA was using to respond to enquiries.
- 5.36 At the time of increased media speculation around the 20 and 21 December, AFSSAPS stated (including in communication with the MHRA as mentioned above) that it was awaiting the advice of the French National Cancer Institute (INCa) before advising on the need for explantation. A report<sup>iv</sup> published by the French government in February 2012, covering the events leading up to 23 December 2011, states that on 5 December the French General Directorate of Health had asked INCa to set up an expert group to 'recommend the strategy to be adopted by healthcare professionals'<sup>v</sup> following the death of a woman with PIP implants from lymphatic cancer. The French Ministry for Health established another 'monitoring' committee on 7 December which met for the first time on 14 December, the same day as another internal 'supervisory' committee was set up within AFSSAPS.
- 5.37 Following a conversation with AFSSAPS on 22 December, MHRA officials concluded that the French were likely to advise routine removal of PIP implants. On the basis of discussions with other EU countries they concluded that the French were taking a different approach to other member states, and that the lack of any new evidence meant the UK professional bodies would support maintaining the current advice that removal

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was not necessary unless there was evidence of a rupture. DH Ministers and the NHS Chief Executive's office were informed of this assessment, and contact was again made with major UK private providers to update them on the position.

- 5.38 The Secretary of State for Health spoke directly to the French Minister of Health on 22 December to underline the high level of concern in the UK and ask that the French authorities share their evidence for their recommendations as quickly and fully as possible.
- 5.39 AFSSAPS officials took part in the meeting of INCa's expert group on 22 December and INCa's advice was published on 23 December, stating there was no evidence of a link to cancer with PIP implants. It further stated "There is currently no justification for an urgent removal of these implants, but the experts have pointed out the risk of premature rupturing and the lack of certainty regarding complications linked to the irritating nature of this gel. In the absence of any symptoms, it is recommended that the recommendations of the AFSSAPS be followed for monitoring patients, ie a clinical and ultrasound examination every six months, specifically targeting the breasts and the axillary ganglion regions. In the event of any abnormal symptoms, a specialised consultation is recommended."<sup>vi</sup>
- 5.40 However, on the same day the French Ministry of Health announced its recommendation that all women with PIP implants should have them removed on a preventative, non-emergency basis. They advised that there was no increased risk of cancer, and that any risk came from ruptures which may lead to inflammatory reactions. This recommendation does not appear to be directly derived from the report of the INCa expert group, although a summary version of the report referred to in paragraph 5.31<sup>vii</sup> stated that "Following the first meeting of this monitoring committee [the one established by the French Ministry for Health on 7 December, which met on 14 December] and having taken note of the advice of the experts assembled by INCa, the [health ministers] declare that they wish the explantation of implants... to be systematically recommended...even where there are no clinical indications of deterioration of the implant..."<sup>viii</sup>
- 5.41 A further EC-led teleconference was held after the French announcement on 23 December, following which MHRA officials reported to Ministers, the Devolved Administrations and external stakeholders that the French had not provided any new evidence and other EU states had indicated that they would not be adopting the French position. The MHRA also had direct contact from the Australian competent authority seeking information on whether the MHRA would be changing its advice on implant removal. The MHRA's Clinical Director for Devices was in contact with Professor Kay over this period to inform clinical decisions on the implications of the French position.
- 5.42 The MHRA issued a further press statement making clear that it was not recommending routine removal of PIP silicone implants in the UK, based on the evidence and expert advice. The press release stated that there was no evidence of an increased risk of

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cancer in women with these implants and no evidence of disproportionate rupture rates other than in France.

- 5.43 Later that day, the Chief Medical Officer wrote to GPs, NHS Medical Directors and plastic surgeons relaying the MHRA's advice and providing a link to the MHRA press statement.
- 5.44 Subsequent to the events on and around 23 December, DH Ministers took a decision – informed by concerns about levels of anxiety among UK women with PIP implants – to commit that the NHS would contact patients who had received a PIP implant in the NHS and ensure they were offered information and advice, and further procedures subject to clinical need and individual wishes. Ministers stated that they expected private sector providers to take similar action.
- 5.45 **There is little doubt that the French government's change of policy in December 2011 came as a surprise to the MHRA and other competent authorities. The MHRA, in common with most other EU competent authorities, concluded that the French authorities had not produced new information to justify a policy of routine removal of PIP implants, and issued prompt advice to this effect. The Interim Report of the Expert Group on PIP implants, chaired by Sir Bruce Keogh and published on 6 January 2012, subsequently endorsed MHRA's conclusion that there was no evidence of a specific safety concern identified that would require a recommendation of routine removal of PIP implants. We have found no evidence to support a different conclusion. The Expert Group also endorsed the subsequent policy response by DH Ministers, recognising that it took account of levels of anxiety among women who had received PIP implants in good faith.**

## Communications

- 5.46 During the period March 2010 to December 2011, the MHRA issued frequent communications in the form of three Medical Device Alerts<sup>ix</sup>, five press statements<sup>x</sup> and individual correspondence. Key formal communications are documented in the timeline at appendix 1. At several points, the MHRA had to issue formal communications at very short notice.
- 5.47 There is no evidence to suggest that the advice and information communicated at various points up to 24 December 2011 was other than appropriate and accurate. However, some commentators have criticised the MHRA for not making greater and more co-ordinated efforts to ensure that information reached people with a direct interest in it, specifically providers, health professionals and affected women. There is a perception that there were relatively long periods of time when little or no information was communicated publicly. It is important to note that ongoing responsibility for the care of individual women with PIP implants rests with the providers and clinicians who initially treated them, and that it is these surgeons and clinics who should hold details of the women who have PIP implants. It was, therefore, appropriate for them to contact women directly if necessary. The MHRA had (and has) no way of communicating

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directly with women who have received PIP implants, and no record of who they are. Indeed it would have been inappropriate and unrealistic for MHRA to have tried to collect patient-identifiable information for this purpose. Its efforts to communicate appropriate information to affected women therefore relied on a combination of action on the part of health professionals and press coverage. That said, as indicated in recommendation viii, we feel there is scope for Sir Bruce Keogh's review to investigate the re-establishment of a more effective Breast Implant Registry and to look at its applicability to other higher-risk medical devices. It is possible that a registry could assist in facilitating direct contact with affected patients, provided this can be done without compromising patient confidentiality.

- 5.48 The MHRA produces a booklet providing general information for women considering breast implants, which is available on its website. This was first produced in April 2000 and most recently updated in April 2011, though because of its focus on women considering new implants it does not specifically detail advice for women who already have PIP silicone implants.
- 5.49 The MHRA's communications response to the events of March 2010 and the months following has been one focus of comment, for example on the extent to which the MHRA took action to ensure that affected women were kept informed. We have already noted that the substance of the message the MHRA communicated at this time, and prior to the availability of the results of toxicology testing, appears appropriate. The evidence did not support advising clinicians to make contact with all women with PIP implants, or advising women to seek clinical advice unless they had concerns (for example that an implant may have ruptured). The MHRA remained in contact with providers and professional bodies to keep them apprised of progress on toxicology testing, and responded to enquiries from individual women who contacted it during this period. The MHRA also corresponded with individual providers on specific issues, such as the management of PIP implants that had been removed.
- 5.50 However, bearing in mind the relatively large number of women affected a higher level of proactive public communication could have been helpful, particularly during the period when the results of toxicology tests were awaited. At its most basic, this might have taken the form of periodic updates to the information on the MHRA's website to indicate the likely timescale for availability of results. Also, as has been demonstrated by the public concern since the French recommendation for routine implant removal in late 2011, a large number of women (around 40,000) have been exposed to high levels of anxiety and uncertainty. The size of this group alone suggests that improved communication activity both before and after the results of any testing could have had significant benefits. While it is the case that the results of the toxicity testing will have addressed many anxieties, there remained a high likelihood for misinformation and misunderstanding to be circulating amongst affected individuals, through social networking and other routes. There were also potentially individuals who remained unaware of any issues with PIP implants. A more proactive and creative approach to

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interaction with affected women, perhaps through less traditional routes of communication such as social networking, could have prevented some of the concern that was generated in late 2011.

- 5.51 The MHRA was also under significant pressure to comment publicly on press speculation about potential French regulatory action in the run up to 23 December. Given the limited information the Agency received from the French authorities, and the fact that it could not pre-empt a formal decision or announcement regarding the French position, it is difficult to see how it could have acted any differently in the days immediately preceding the French statement.
- 5.52 Cascade communication of information to health professionals, via the relevant professional bodies, appears to have worked as it should, though there are some concerns that not all relevant clinicians were members of the relevant bodies and so may not have received communications through these routes. Information was also disseminated, as with any Medical Device Alert, through the Central Alerting System. This relies for its operation on the actions of CAS liaison officers in individual NHS organisations and through relevant private providers being signed up to receive email alerts. We have found no evidence that this system failed to disseminate the information fed into it appropriately.
- 5.53 Public communications and formal communications with provider organisations therefore also have an important role to play. The MHRA issued press statements on a number of occasions over this period, and there was national and international press reporting on PIP implants at the end of March 2010, and periodically thereafter until the widespread coverage in December 2011. Health care professionals have a responsibility to keep themselves up to date with issues affecting their practice. It was reasonable to expect health professionals to be aware of the advice the MHRA was issuing, and this generally appears to have been the case.
- 5.54 There was very frequent, less formal communication with professional bodies and with the private provider organisations whose surgeons had implanted the great majority of these devices, both to relay and to seek views. This important communications work was largely undertaken through the clinical team in the MHRA's Devices Directorate, with much communication being undertaken by the Clinical Director through individual and small group e-mails. This level of clinical involvement in communications was entirely appropriate, particularly where links were being made with professional bodies and / or concern specific clinical advice and judgements, but it placed a heavy burden on a few key individuals and their direct contacts.
- 5.55 There were some occasions when lines being used publicly by the MHRA and some professional bodies could have been better co-ordinated to promote consistent advice on the management of affected patients, though of course the MHRA cannot itself control statements made by other organisations. While generally appreciative of the efforts the MHRA made to keep them informed of developments, over and above

published communications, some private providers also expressed a desire for a single co-ordinated communications channel between themselves and the MHRA on PIP issues.

- 5.56 As well as communicating information actively to professionals, providers and the press, the MHRA made a significant amount of information available on its website. However this web-based information has to serve a variety of audiences, which may affect its immediate accessibility to the public, and it is not always easy for an infrequent, non-expert user to find information most relevant to them. In cases where advice remains unchanged for some time (as with the MHRA's advice while toxicology testing was underway) it would be helpful to indicate from time to time that the information has been reviewed and remains the most up to date available.
- 5.57 **Taken as a whole, we believe there is scope for the MHRA to use its experience with PIP implants to improve the way the organisation manages and co-ordinates communications activity, not just at the point at which a piece of formal advice needs to be issued but in terms of managing a series of communications with diverse audiences – specifically including concerned members of the public – on an ongoing set of events.**

**Recommendation ix:** *The MHRA should review and further develop its communications capability to ensure they can rapidly establish and provide centralised communications regarding device alerts and related issues on an ongoing basis. This should be a proactive capability serving the needs of patients, professionals and the press / public. It should regularly and simply update interested parties around progress and current information on specific safety concerns, anticipating areas of anxiety or uncertainty and managing the information and misinformation that can circulate around safety concerns. It should also constitute an easy to access source of data for concerned individuals.*

## Decision-making

- 5.58 Decisions on issues relating to events of PIP implants from March 2010, including public statements, were in the main taken by senior clinical, technical and administrative staff in the MHRA's Devices Directorate, consulting frequently with external experts including relevant members of the Committee on Safety of Devices (CSD). Consultation with the CSD was generally through direct communication with specific members who had the relevant expertise, rather than through formal meetings of the full committee. This is understandable given that advice was frequently required at short notice and that CSD membership includes experts in a number of specific fields. The Agency's Chief Executive was directly involved at key decision-points, including in high-level communications with other regulators. All submissions to Ministers were cleared by the Chief Executive, and from March 2010 the MHRA Board received periodic reports on PIP implants (though the Board does not have a role in decisions on the handling of specific incidents).

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- 5.59 The use of expert advice on specific issues is set out earlier in the report. The MHRA appears to have sought appropriate advice from respected sources, including members of CSD, the main professional bodies and the National Clinical Director for Imaging. The Chief Medical Officer issued advice to health professionals in December 2011 and saw copies of advice to Ministers, but was not directly involved in specific decisions about the evidence relating to PIP implants. While there were some exceptions at particular points in time (for example the BAAPS position on ultrasound in autumn 2010), it appears that the specific clinical advice the MHRA was issuing was consistent with the views of UK experts and the positions adopted by most other regulators.
- 5.60 Ministers appear to have been kept appropriately informed about events, receiving submissions at key points between March 2010 and December 2011 (see the timeline at appendix 2). Most submissions were for Ministers' information, with only one, regarding the MHRA's publication of toxicity results in September 2010, asking for Ministerial approval of the MHRA's proposed actions. With the exception of one submission sent in the pre-election period these submissions were noted or actioned quickly by Ministers. A submission "for information" provides Ministers with an opportunity to raise questions and concerns. Earl Howe posed questions in response to a submission in October on the French advice following toxicology tests, and received a prompt response which he noted.
- 5.61 We note that the post of Director of Devices at the MHRA, a post reporting to the Agency Chief Executive and having strategic oversight of the Agency's work on medical devices, was vacant for 17 months up to February 2012.

**Recommendation x:** *While we found no evidence of a direct impact in this case, the MHRA Board and Department of Health should ensure that key strategic posts in the organisation do not remain unfilled for long periods of time.*

## 6. Policy implications

This section considers the following part of the review's terms of reference:

**“The review will advise the Secretary of State on what lessons can be learned for application should similar circumstances arise in the future, and on implications for UK input to the ongoing review of the European Medical Devices Directives.”**

### European regulatory activity

- 6.1 The regulatory system for medical devices operates under a common European framework. The scope for improvement and reform therefore needs to be considered at this level, as well as in relation to the operation of arrangements in individual member states. In addition to the opportunities for learning on operational issues, discussed in earlier sections of this report, the experience with PIP silicone implants raises important issues relating to regulatory policy.
- 6.2 The European Commission is already undertaking a review of the Medical Devices Directives, which govern device regulation in the EU, following an initial consultation in 2008. Proposed revisions are likely to include provisions for stronger supervision of notified bodies, improved vigilance systems, clinical investigations and traceability of implanted devices. The Commission has indicated that it will review and “stress test” its proposals in the light of the PIP experience, to establish whether further lessons can be drawn to reinforce work on the Directives. We expect that the Commission will publish the results of this “stress testing” shortly, followed by final legislative proposals. Any revisions to the Directives are unlikely to come into force before 2015 at the earliest.
- 6.3 The Commission has also proposed that it should work with member states to develop a joint plan for short-term actions, focused on improving the implementation of existing regulatory requirements. Elements of this plan are likely to include measures to;
  - ensure notified bodies are meeting current requirements;
  - require fuller use of existing provisions for unannounced inspections and sample testing;
  - improve information-exchange and co-ordination of incident analysis among competent authorities;
  - reinforce market surveillance activities by competent authorities; and
  - improve the traceability of devices to support long-term monitoring of their safety and performance.

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- 6.4 These proposals are generally consistent with views the MHRA, as the UK regulator, had been advancing at European level about priorities for improving the operation of the regulatory system for medical devices.
- 6.5 While regulatory systems can aim to deter, and minimise the risk of, deliberate subversion and fraud, it would be unrealistic to expect any regulatory system to be completely impervious to deliberate and potentially criminal actions intended to undermine or bypass its operation. It is particularly important that any regulatory response to the PIP scandal is evidence-based. **There is no evidence, or good reason to believe, that a fundamental system change (such as a shift to the model operated in the EU for pharmaceuticals or that used in the USA for higher-risk categories of devices both of which involve lengthier pre-market phases) would have prevented the deliberate abuse of the system that took place in this instance.**
- 6.6 As a point of principle, the best response to subversion of existing regulatory requirements is unlikely to be a fundamental change in those requirements, and in that context the immediate focus of the Commission's proposals makes good sense. Better implementation across Europe of post-marketing surveillance arrangements may provide greater deterrent to any future attempts at deliberate fraud, and should offer patients improved reassurance.
- 6.7 With regard to the Commission's plans for regulatory reform, we believe that, in line with its responses to official consultations to date, the Government should continue to support moves to improve oversight and co-ordination of the regulatory system. We have also heard that current constraints on information-sharing can hamper both international co-operation and work with health professionals to assess and investigate potential problems. Therefore moves to facilitate easier information-sharing, among competent authorities and more widely, should be supported. Relevant issues for the ongoing review of the Devices Directives are likely to include mechanisms for improving the performance of notified bodies, strengthening requirements on manufacturers to carry out post-market surveillance of devices (in particular for higher-risk devices), improving the consistency of implementation of the directives by member states and improving information-sharing among European competent authorities. The detail of implementation will be important in ensuring that improvements are deliverable and have the maximum traction.

**Recommendation xi:** *The MHRA and Government should fully support efforts initiated by the European Commission to improve the operation of the regulatory system, with particular regard to higher risk devices, within the current legal framework and in advance of any specific legislative proposals the Commission brings forward. In particular, they should press for early adoption of proposals for a single European reporting portal to provide a central repository for information on device adverse incidents, accessible to all EU competent authorities. They*

*should also press for the establishment of frequent routine teleconferences, facilitated by the Commission, to make it easier for EU competent authorities to discuss specific areas of concern regarding medical device safety and regulation on an ongoing basis, in order to improve European Co-ordination.*

**Recommendation xii:** *The MHRA and Government should endeavour to ensure that future reform of devices regulation at European level is based on a rigorous and transparent assessment of the evidence. Any implications for the work of the MHRA should be carefully costed and the Agency supported to ensure that it can discharge its functions effectively.*

## The MHRA

6.8 This review has not found evidence of significant errors or omissions on the part of the MHRA, or the wider Department of Health, in its handling of work on PIP silicone implants. Indeed there are some positive points, such as the MHRA's prompt action to commission additional toxicology tests in the summer of 2010 when it became apparent that the promised French tests were significantly delayed. However, any analysis of a series of events of this length, complexity and controversy can be expected to generate lessons for future practice. It is important that learning opportunities, including the operational recommendations highlighted in section 4 of this report and findings from the MHRA's own "lessons learned" exercise, are properly recognised and subsequent action properly implemented and embedded. While this review is very specifically focused on the experience of PIP silicone implants, it is important to recognise that it also provides relevant context for future, wider work to assure and develop the MHRA's capability.

**Recommendation xiii:** *The Department should ensure that a focus on continual improvement in device vigilance is an explicit component of the MHRA's annual business plan, and that arrangements are in place to monitor the delivery and impact of agreed improvements.*

**Recommendation xiv:** *The Department of Health should ensure that the actions and lessons from the events surrounding PIP breast implants are taken into account and acted on by the MHRA. This should be assured through routine sponsorship arrangements and in the Department's Performance and Capability Review of the MHRA.*

6.9 The events surrounding PIP implants involved much interaction between the MHRA, provider organisations, professionals and patients. Taken as a whole, we believe that these interactions suggest a continuing need to nurture a shared understanding and common purpose with regard to regulatory activity on higher-risk medical devices. It is also important to recognise that the regulator alone cannot ensure optimal working of the vigilance system: as we have already noted, front-line health professionals and provider organisations have a central role in identifying and acting on patient safety issues, and they must see themselves as full partners – along with the devices industry – in work to that end. We heard that professional attitudes to device incident reporting

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are changing for the better, though there remain concerns about levels of professional awareness about what should be reported and how. Progress needs to be sustained through continued partnership working with relevant professional bodies and regulators. Again, regulatory provisions that support better exchange of information will be helpful in encouraging a culture of openness and reporting.

**Recommendation xv:** *All parties - healthcare professionals, providers and patients, as well as industry - must be involved in the vigilance system as equal partners with the single aim of reducing the risk of harm to patients from medical device incidents. MHRA should therefore continuously review its activities to ensure that everything it does is consistent with this aim, and that it promotes this shared aim amongst all those involved in medical device vigilance.*

# Appendices

## 1. Chronology of key events

Date	Event
January 1993	First European directives regulating the marketing of medical devices start to come into effect.
January 1995	The Active Implantable Medical Devices Directive comes into force.
22 October 1997	TUV Rheinland certifies PIP silicone implants as a Class IIb device.
June 1998	The EU Medical Devices Directive comes into force.
July 1998	<p>Publication of the ‘Silicone Gel Breast Implants’ – the Report of the Independent Review Group.</p> <p>This concluded there was no evidence for unexpected or unanticipated adverse health impacts from silicone breast implants. It also made a number of recommendations including how the risks of implants should be communicated, adverse incidents reported and implants registered.</p>
June 2000	The EU In Vitro Diagnostic Medical Devices Directive comes into force.
December 2000	MDA (now MHRA) issues Medical Device Alert for the voluntary recall by PIP of their hydrogel breast implants.

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	<p>'The manufacturer has, as a precautionary measure, voluntarily withdrawn PIP Hydrogel breast implants from the UK market until sufficient information to address MDA's concerns is available.'</p> <p>'Women who are worried should be offered a consultation. It should be emphasised that a definite risk has not been identified.'</p>
18 April 2001	Following extensive exchanges between AFSSAPS and PIP regarding testing and safety data, AFSSAPS decide to allow the marketing of PIP's silicone breast implants in France.
5-6 June 2001	AFSSAPS inspect PIP manufacturing site, finding in particular concerns about the manufacture of the NUSIL implant filler from its components ( <i>"the ratio of the 2 components in the mixture had not been respected"</i> ). Only one batch is noted to be affected and this is recalled on 27 June by PIP. There also follow some discussions about the use of gluteraldehyde to disinfect PIP implants.
14 December 2001	Following the June inspection and extensive interactions between PIP and AFSSAPS, particularly around sterilisation techniques, AFSSAPS' final inspection report states <i>"All the inconsistencies of the present report have been dealt with"</i> .
June 2002	The EU Medical Devices Directives incorporating stable derivatives of human plasma come into force.
16/18 July 2002	A recertification audit of PIP is carried out by the notified body, TÜV Rheinland. This leads to a second certificate relating to the comprehensive system of quality assurance for PIP silicone implants being issued on 17 October 2002.
8 December 2002	A surgeon writes to MHRA informing them of his recent treatment of a patient with both PIP silicone breast implants, both of which ruptured within 2 years of implantation. This is the first direct notification to MHRA from a surgeon of an adverse incident involving PIP silicone implants of which we are aware.

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3 February 2003	Breast implants are reclassified as class III medical devices.
27 February 2003	MHRA writes to PIP referring to a letter sent by MHRA to PIP in August 2002. This original letter contained a number of queries on which MHRA is still awaiting responses. The latest letter refers to a number of adverse incidents including some involving PIP silicone breast implants.
11 April 2003	Two " <i>recapitulation summaries</i> " are produced by AFSSAPS' own laboratories regarding their analysis on filler gels contained in various brands of breast implants. These summaries indicate that the results obtained for PIP are similar to those of other manufacturers. These analyses thus suggest that only NUSIL gel was used for the implants tested (according to AFSSAPS interpretation).
17 July 2003	<p>MHRA writes to PIP as a new Medical Devices Specialist has taken over responsibility for breast implants and reviewed PIP's incident files. In the letter the Devices Specialist writes <i>'in the course of taking over this responsibility, I have reviewed all the PIP files that we currently have open and have found that we have not received responses to the majority of questions raised in [our] letter [of 27<sup>th</sup> Feb 2003]. I am also aware that many of these questions were originally raised in [the] letter to you last August, clearly this lack of response is unacceptable and requires immediate action'</i>.</p> <p><i>'You will have noticed from the list of incidents above that a large number relate to the hydrogel implants. You will also have noticed that the majority of questions that I have raised were originally asked ... in August 2002 as well as in [the February 2003] letter. The fact that you have failed to respond to these questions is clearly unacceptable and you should provide a response immediately and by the <u>29<sup>th</sup> August 2003 at the latest.</u>'</i></p>
30 July 2003	PIP writes to MHRA with a response addressing the queries raised in MHRA's letter of 17 July 2003.
2004 (precise date)	PIP silicone breast implants are re-certified as a Class III device following re-classification of all implants in 2003. Details from TUV

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unknown)	<p>Rheinland obtained in 2012 state that the clinical data in the Design Dossier for PIP silicone implants was reviewed and “<i>the clinical evaluation was based on the following:</i></p> <ul style="list-style-type: none"> <li>• <i>a retrospective study (Retrospective clinical study on Silicone Gel Pre-Filled Breast Implants manufactured by Poly Implants Prothèses in Australia).</i></li> <li>• <i>equivalence/literature, supported by the Independent Review Group (IRG, USA) report and the Institute of Medicine (IOM, UK) report (NUSIL material),</i></li> <li>• <i>In addition it should be considered, that these implants have been on the market since 1997. Therefore PIP presented data from their complaint analysis to support the clinical evaluation considering an ongoing study at that time in France.”</i></li> </ul>
2 July 2004	MHRA writes to PIP on a number of issues including reference to at least 4 silicone implant ruptures.
3 August 2004	PIP write to MHRA addressing MHRA’s letter of 2nd July 2004. PIP confirm that they are going to implement electron microscopy analysis of rupture implants soon.
22 September 2004	PIP writes to MHRA regarding 5 adverse incident reports.
25 October 2004	MHRA writes to PIP about a number of adverse incident reports, including 4 involving silicone implants.
9 December 2004	PIP reply to MHRA’s letter of 25 October. Further information is given regarding the four silicone implant incidents. Three involve envelopes being ‘totally cut’, and PIP say it’s impossible to find the origin of the defect. The involves a suggestion of ‘underfilling’.
2005	The UK Breast Implant Registry is closed due to difficulties in obtaining agreement from sufficient women to participate in research, which meant that any conclusions drawn were

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	scientifically invalid.
18 January 2005	MHRA writes to PIP asking for overall figures for sales, incident reports, ruptures, cuts, tears, leakages, intracapsular fluid and other reported adverse health effects in relation to PIP silicone breast implants. The letter also discusses 22 individual silicone implant incident investigations. Further information is requested for 16 and 5 were closed. A copy of the silicone implant product literature and instructions for use is also requested.
15 March 2005	PIP write in response to MHRA's letter of 18th January 2005. Information is provided in response to MHRA's queries including figures on sales and various types of failures from 01/04/1999 to 31/12/2004.
15 August 2005	An MHRA Breast Implant Group meeting is held where the minutes note that a " <i>trending protocol [is] needed for all breast implants...This should include trigger levels and an assessment of existing incidents. ACTION: carry out trend review &amp; arrange meeting to discuss in November 2005</i> "
4 October 2005	An MHRA Medical Devices Specialist writes to a surgeon in relation to information he has previously provided regarding two breast implant incidents, asking for his views on PIP silicone implants, particularly on the strength of the implant shell and whether the type of damage he has seen was associated with the patch.
15 November 2005	MHRA undertakes its first 'trend review' for breast implants. All Breast Implant incidents are reviewed from 01/11/03 to 31/10/05. This reports that while another brand of implants has the greatest number of reported ruptures ' <i>the number of ruptures with PIP silicone filled implants is higher than expected</i> '.
6 December 2005	A Breast Implant Group meeting is held, the minutes of which note the " <i>trend review [was] produced - no previously unidentified trends found</i> ' PIP is not mentioned specifically

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14 February 2006	An MHRA Medical Devices Specialist chases a response from the surgeon written to in October 2005 asking for his comments on PIP implants.
15 February 2006	<p>MHRA writes to PIP regarding (among other things) 20 adverse incident. This letter asks further questions in relation to 5 incidents, chases further information on 9, updates PIP on one and closes 5 investigations. MHRA specifically asks: <i>“Your analyses have shown that for 10 of these reports the cut/tear extends along the edge of the patch. Have you considered the possibility that the area where the edge of the patch contacts the implant shell is inherently weak and is the initiation point for the damage seen?”</i></p> <p><i>“I plan to contact a number of surgeons who have removed implants that have been ‘totally cut’ to obtain their opinions. I will keep you informed.</i></p> <p><i>“Additionally, how long do you consider that it is acceptable for a silicone or saline filled implant to last?”</i></p>
23 February 2006	A surgeon responds to the Medical Device Specialist’s original letter of 4 October 2005 saying he can’t be sure whether the patch is causing rupture. He offers to analyse his patient data saying to clarify this point; <i>‘it would be a feasible exercise because my series goes back a long way and it includes large numbers of implants [of different brands]..if you wish to make closer analysis of ruptured implants I would be very happy to do so but it may take sometime.’</i>
22 March 2006	A solicitor emails MHRA regarding a number of people he is representing against PIP in relation to a hydrogel implants that he has been in contact with MHRA about previously. He also mentions he has <i>“non hydrogel cases against PIP.”</i>
9 May 2006	MHRA writes to PIP sends chasing the letter they sent on 15 February 2006.

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11 July 2006	MHRA writes to PIP again chasing the letter originally sent on 15 February and chased on 9 May.
13 July 2006	MHRA receives letter from PIP dated 9 July, addressing MHRA's letter of 15th February 2006. This response includes information about a modification to PIP's gluing system around the patch carried out in 2001 due to PIP noticing an issue with patch 'detachment'. PIP haven't noticed further patch detachment to date but commit to having ' <i>a closer look at the ruptures located around the patch</i> '. Further details of 20 incidents were discussed, and an update on the plans for electron microscopy provided.
25 July 2006	MHRA conducts a breast implant trend analysis, which reports that there appears to be an ongoing issue with relatively high PIP silicone implant rupture rates, possibly associated with the patch area, and that MHRA continues to pursue the possibility that the patch represents an area of weakness on the shell.
August 2006	Lahiri and Waters publish a report in the Journal of Plastic, Reconstructive & Aesthetic Surgery reporting a case of PIP silicone implant rupture and their professional concerns about PIP implants.
13 September 2006	MHRA writes to another surgeon asking for views regarding their experiences with PIP silicone implants, particularly associated with the patch area.
15 September 2006	MHRA writes to a third surgeon asking for views regarding their experiences with PIP silicone implants, particularly associated with the patch area.
28 September 2006	MHRA speaks via telephone to the surgeon they wrote to on 13 September. He reported that he had a slight suspicion that there was higher rupture rate with PIP implants. He asked his theatre manager in 2004 to review PIP rupture data, but found it was similar to other manufacturers. He no longer uses PIP implants however and offers to put together a report of experiences.

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November 2006	MHRA publishes <i>“Breast Implants; Information for women considering breast implants”</i> .
2 November 2006	<p>MHRA writes to PIP in response to their letter of 9 July 06. MHRA ask a number of questions about the changes to patch design implemented in February 2001, including what testing has been carried out and what testing facilities are in place.</p> <p>MHRA also expresses concerns that new microscope facilities have still not been implemented.</p> <p>MHRA requests details of further testing PIP said was planned. 17 individual incidents are discussed.</p>
7 December 2006	A breast implant trend review is carried out by MHRA on all incidents since 1 November 2003. The total number of reports has been consistently reducing since Nov 2004 – partly due to absence of Trilucent reports. The report states <i>‘It appears that some manufacturer’s implants are more prone to rupture than others...Most of the reports involving PIP silicone gel implants involve extensive rupture of the shell’</i> . An issue with high rupture rates in PIP implants is noted as ongoing and has been carried over from previous review. The report also notes PIP has agreed to investigate the issue further.
11 December 2006	A Breast Implant Group meeting is held where the 7 December trend review is considered. No PIP saline implant-specific actions are recorded.
18 December 2006	MHRA sends a chaser letter asking PIP for a reply to their 2 November letter.
19 December 2006	PIP respond to MHRA’s letter of 2 November. This response discusses MHRA’s concerns with the implant patch, providing further information on PIP’s patch design and states microscopy will be implemented by January 2007. New sales and failures rates are provided (1999-2005). Breast implant product literature is also provided and 17 incidents are discussed.

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<p>22 December 2006</p>	<p>MHRA receives a response from the surgeon they wrote to on 15 September 2006. He writes <i>'I do agree with you that there appears to be a definite problem with these implants. I personally have exchanged about twelve sets of implants in the last year alone from my own patients who have in fact had the implants for less than two/three years...In addition...I have had countless PIP implants break in my hand whilst demonstrating these implants to patients...As a result of these failures I have in fact now changed my implant manufacturer despite using the PIP implants for nearly ten years...My own personal feeling is that these implants should be withdrawn from the market, pending further tests on them...If you require any further information, I would be more than happy to provide this for you and assist in the matter.'</i></p>
<p>2 February 2007</p>	<p>MHRA speaks with the practice nurse for the surgeon who wrote to them in December 2006. The nurse states they have had 3 more ruptures but want to know what to do with the implants as they are not happy with PIP's previous analysis. MHRA say they cannot test the implants or fund independent testing but encourage the nurse to reporting these incidents to MHRA using MHRA's reporting form.</p>
<p>22 February 2007</p>	<p>A MHRA Medical Devices Specialist sends an internal email to MHRA's Compliance unit raising concerns with PIP. This states <i>'We would like to ask your opinion on raising the following issues with either the notified body or with BfArM [German Competent Authority]: slow vigilance reporting... inappropriate conclusions... We are continuing to pursue various other issues such as the adequacy of PIP's analysis of returned implants and a possible quality issue with the implant shells, but these are being handled through the incident investigation route.'</i></p>
<p>27 March 2007</p>	<p>MHRA writes to the surgeon who offered them more information on his experiences with PIP implants when they spoke to him on 28 September, requesting that he send them the information he previously offered.</p>
<p>3 April 2007</p>	<p>MHRA writes to PIP with various adverse incident report updates. MHRA further acknowledges the information provided in PIP's letter of 19 December 2006 relating to the patch area.</p>

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	<p>MHRA further asks for PIP's analysis of the time-to-failure data for their explants, the outcome of PIP's promised "closer look" into the issue of ruptures including further information on a possible natural stress line that PIP have previously identified, and details of any corrective actions that may reduce this problem.</p>
20 April 2007	<p>B Berry, a surgeon, reports in the Journal of Plastic, Reconstructive &amp; Aesthetic Surgery professional concerns with PIP silicone implants following an implant rupture. This refers to the earlier Lahiri/Waters article.</p>
25 April 2007	<p>MHRA's vigilance section raise MHRA's Medical devices specialist's concerns regarding PIP in writing with the German competent authority. MHRA asks the German competent authority to contact TUV Rheinland, the relevant notified body for PIP, to ask about these issues.</p>
21 May 2007	<p>The German Competent Authority inform MHRA that TUV Rheinland will look into the problems that MHRA has identified during the reclassification audit planned for June 2007.</p>
27 May 2007	<p>PIP write in response to MHRA's letter of 3 April. PIP confirm that they are now using a new microscopy technique. PIP discuss further the total shell ruptures/patch ruptures, describing a stress concentration that may occur on the patch/shell border and may give rise to failure in this area over time. They state that they are currently studying this to reduce the problem of patch rupture. A total of 13 files were discussed.</p>
30 May 2007	<p>MHRA undertakes a breast implant trend review, which notes ongoing concerns with PIP's apparent higher rupture rate, concerns over the implant shell and the association with the patch, and that concerns about the provision of information by PIP have been raised with the notified body.</p>
23 July 2007	<p>MHRA writes again to the surgeon they wrote to on 27 March 2007 further requesting a report of his experiences with PIP silicone implants. The letter states that if no response is received within 4 weeks MHRA will assume the report will not be</p>

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	forthcoming.
13 August 2007	MHRA writes to PIP requesting further information regarding the PIP study to address a possible 'stress concentration' on their implants' shells. Nine individual incidents are also discussed. MHRA also requests PIP's views on the Berry paper published in April which questioned the reliability of PIP implants. MHRA suggests that PIP's higher failure rate should be mentioned in PIP's Instructions for Use literature to inform potential customers.
17 September 2007	MHRA sends a chaser letter to PIP asking for a reply to their 13 August letter by the end of the month.
30 September 2007	<p>PIP write to MHRA regarding MHRA's letter dated 13 August 2007. PIP describe their study to reduce difference in thickness between the patch and shell to address any possible shell weakness and that they are undertaking a feasibility test for this design change, which is expected at the end of 2007. Nine individual incidents are discussed including 2 where PIP say the implant split on insertion. PIP also provide a list of 'total' rupture incidents involving PIP silicone implants.</p> <p>PIP stated their 0.7% rupture rate at 5 years post-implantation is lower than other manufacturers, not higher. Regarding the Berry article mentioned in the previous letter from the MHRA, PIP say the author's remarks are without basis because no quantitative data were given. PIP also provide MHRA with in-vitro mechanical data and cycling stress/fatigue data.</p>
31 October 2007	MHRA writes to PIP, thanking them for their list of silicone implant total rupture reports. The MHRA notes in this information a pattern of higher failure rates between 2-3 years and 5-6 years and ask PIP to check if this pattern is also exhibited in the worldwide data. Four individual adverse incidents were discussed.
5 November 2007	MHRA receives an independently commissioned report regarding faulty implants was provided by an affected patient. This patient had two consecutive PIP implant ruptures, both in the right breast. The report concludes that the cause of failure was implant design and service loads stresses, which were beyond the fatigue

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	<p>strength of the material used in the implant shell.</p>
14 November 2007	<p>MHRA's Compliance unit receives feedback from the German Competent Authority about the outcome of TUV Rheinland's recertification audit of PIP. The German Competent Authority states <i>'The examples from MHRA were clearly to [sic] late reported, although the internal evaluation to the corrective actions had taken place. The cause was finally because of individual mistakes.'</i> <i>'The staff in the company responsible for vigilance were competent.'</i></p> <p>The response also suggests improvements have been made to PIP's vigilance system.</p> <p>MHRA replies saying 'this reassures us that the process is now under control'.</p>
23 November 2007	<p>MHRA carries out a breast implant trend review. This again notes that the distribution of ruptures is not equal between manufacturers. It includes a time to rupture graph for PIP's reported ruptures which is suggestive of an early rupture peak for a small number of implants at 4 years post-implantation. This further reports <i>'PIP estimated a rate of failure of their silicone implants of 0.5% over 3 years of implantation, which is in the same range of failure rates of similar implants of other manufacturers on the market.'</i></p> <p>This review also notes issues of vigilance reporting and provision of accurate investigation conclusions were taken up with TUV Rheinland who reported back that <i>"the root cause of these responses from PIP were due to individual mistakes and that current staff in the company responsible for vigilance are competent. All vigilance cases from 2007 were processed on time and been reported, which is in agreement with MHRA's experience"</i>.</p>
19 December 2007	<p>A Breast Implant Group meeting is held. The minutes note that the <i>"Breast implant trend reviewed in November 2007 noted similar levels of silicone rupture reporting as in May 2007 review. The increase in May 2007 was due to an increase of PIP reporting in 2007 as confirmed by TUV following their last NB audit. A pattern on timing of PIP silicone ruptures seems to have</i></p>

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	<i>emerged and [is being] taken up with PIP.”</i>
21 December 2007	PIP write to MHRA regarding MHRA’s letter dated 31 October 2007. They inform MHRA that the thickness of their implant patch is changing from 1 <sup>st</sup> Jan 2008. PIP dispute MHRA’s observation that there is evidence of an early rupture peak in their data. They refer to the fact that the overall number of incidents used to construct this analysis (28) is very small in the context of overall sales (69030) and this ratio of around 4/10000 is the same as in their worldwide data and is too small to allow a trend to be confirmed statistically. PIP also further refer to Berry’s paper, concluding it is a case report of an accepted risk (ie rupture) that they themselves highlight in their product literature.
2008	EU consultation begins on updating the Medical Devices Directive.
13 March 2008	MHRA writes to PIP asking if PIP have considered the need for a Field Safety Notice to be issued given their change to their patch thickness. MHRA also asks for the worldwide rupture figures PIP referred to in their previous response so MHRA can look into the possibility of there being a ‘peak’ of early ruptures.
8 April 2008	PIP write to MHRA responding to MHRA’s 13 March letter – content unknown as MHRA cannot find a record of this response.
28 April 2008	MHRA writes to PIP thanking them for their letter of 8 April. MHRA refers to the worldwide rupture data that PIP have provided, agreeing that in the context of total sales it is difficult to draw conclusions. MHRA do however point out that UK ruptures between 2 and 3 years constitute 50% of the reported worldwide total for early ruptures despite the UK only representing 17% of worldwide sales. MHRA asks for PIP’s comments on this and also ask for statistical data across all reported complications for the UK silicone filled implants and sale figures.
30 May 2008	MHRA conducts a breast implant trend review. This Includes the number of incident reports for breast implants since 1 November 2003 by manufacturer. It states that ‘ <i>As previously, most of the reports involving PIP silicone gel implants involve extensive rupture of the shell, often in contact with the sealing patch on the</i>

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	<p><i>posterior surface...PIP is developing a new design to reduce the thickness between the patch and the shell. The feasibility testing of the prototype is in progress.</i>' The report continues to note that PIP silicone implants appear to have a relatively high rupture rate.</p>
8 June 2008	<p>PIP write to MHRA regarding MHRA's letter dated 28<sup>th</sup> April 2008. PIP discuss UK rupture rates and point out that while the UK may have a relatively high proportion of early 'total ruptures' if all types of rupture are considered, then the proportion of early ruptures in the UK is consistent with the proportion of sales in the UK. PIP also provide the figures on the total number of reported complications in the UK as requested.</p>
5 August 2008	<p>MHRA writes to PIP requesting an update from PIP regarding the change of thickness to the patch and speculating that given the proportion of 'total ruptures' is higher in the UK than expected, might this reflect a UK preference for textured implants? MHRA therefore asks for information on the proportions of ruptures worldwide involving textured implants and updated figures for UK and worldwide partial and total ruptures.</p>
29 September 2008	<p>PIP reply to MHRA's letter of 5<sup>th</sup> August 2008. PIP give an update on the reduction of the thickness of the implant patch. They further discuss the design change involving their implant mould and have decided to abandon these ideas and keep looking for solutions. They are thinking about changing the shape of the patch.</p> <p>PIP also state their data does not support the idea that textured implants are more susceptible to rupture than the other implants, and provide more data on all kinds of implant ruptures.</p>
5 November 2008	<p>An article is published in Journal of the American Medical Association (JAMA) reporting on cases of ALCL in women with breast implants.</p>
20 November 2008	<p>MHRA writes to PIP requesting annual sales and annual rupture figures of all types for the UK over the last 5 years.</p>

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26 November 2008	A breast implant trend review is carried out by MHRA. The high rupture rate with PIP silicone implants possibly associated with patch is carried over from the previous review.
16 March 2009	MHRA sends a chaser email to PIP regarding a response to MHRA's letter of 20 November 2008.
31 March 2009	PIP emails MHRA with a response to MHRA's letter of 20 November 2008. This includes data regarding sales and ruptures for all PIP implants in the UK.
5-8 June 2009	MHRA emails PIP seeking further information following an earlier email [unavailable] regarding 4 ruptures from the same batch of implants. PIP reply clarifying that the rupture rate with the batch is 1.89%.
12 June 2009	<p>MHRA email PIP again noting 4 ruptures in one batch and asking <i>'How does the rupture rate for the 26903 batch compare with the 5 year rupture rate in other batches? Are there any other batches that have similar ruptures rates (within 5yrs)?</i></p> <p><i>'If the high rupture rates are only seen within the 26903 batch I would appreciate if you could inform me of any factors or reasons that you feel have led to this?'</i></p>
25 June 2009	Internal MHRA emails relay information from a theatre manager saying PIP implants are getting a very bad reputation for longevity amongst surgeons and women. He also notes though that increased PIP vigilance is probably leading to more detection of silent ruptures and driving up the number of reported incidents.
30 June 2009	PIP reply to MHRA's email of 12 June saying the rupture rate per batch is acceptable and pointing out that given the size of each batch, a single additional rupture increases the rupture rate by 0.5%. PIP say their average rupture rate is 0.7%, therefore only one additional rupture virtually doubles the rupture rate. The batch MHRA have highlighted has 4 individual ruptures out of 211 implants, which does not to them indicate a fundamental problem

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	with the batch. MHRA's internal discussion of this response indicates PIP's argument may be reasonable but that a further 'time to rupture' analysis is planned by MHRA which should provide more information.
1 July 2009	MHRA carries out a 'time to rupture' analysis of PIP implants suggesting a relative 'peak' in early rupture, within 4 years of implantation. MHRA internal emails indicate they feel the pattern is striking, but that they also need to exclude hydrogel implants and compare the pattern to other implant brands before going back to PIP with this analysis.
August 2009	An internal AFSSAPS document from their medical devices system summarising the vigilance data relating to implantable silicone prostheses, reveals an increase of the number of PIP ruptures, with the deviation starting in 2008, although the level remains comparable to that of other manufacturers.
6 November 2009	MHRA internal emails indicate a Medical Devices Specialist is concerned with the apparent increase in PIP reporting and is looking to determine how much of this observation may be due to better reporting following the action taken by TUV Rheinland in 2007.
10 December 2009	<p>The Executive Director of AFSSAPS emails their devices division, reporting that a breast surgeon he knows informed him of a <i>"recurrent" rupture rate "occurring at an unusual frequency, of unusually early ruptures of implants from the company PIP, compared to the normal profile, where the rate of ruptures develops in a linear manner as the years go by. Several of his colleagues have also observed this, and he himself told me that he had filed medical device vigilance incident reports."</i></p> <p>The Executive Director requests the opinion of the devices division on the existence of a 'signal' which would justify an intervention by AFSSAPS.</p>
15 December 2009	MHRA emails PIP pointing out a significant increase in incident reporting from PIP since 2006 (from 13 incidents in 2006 to 74 to date in 2009) and asking them if this was due to a <i>"change in what is considered reportable by PIP and your notified body in</i>

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	<i>mid-2007 rather than an increase in the number of incidents reported”.</i>
18 December 2009:	<p>PIP is summoned by AFSSAPS to a meeting, for which AFSSAPS has requested that PIP provide:</p> <ul style="list-style-type: none"> <li>– <i>“the list of clients for breast prostheses that are pre-filled with silicone since 2004</i></li> <li>– <i>the origin of the raw materials used for the manufacture of the implants and any changes made to the channel of supply</i></li> <li>– <i>any information relating to a change in the manufacturing process since 2004 (materials, methods, environment etc.)</i></li> <li>– <i>the retrospective report regarding the incidents that occurred in relation to breast implants since 2004, particularly on breast prostheses with textured envelopes that were pre-filled with silicone and, as the case may be, the measures that were implemented to remedy any problems.”</i></li> </ul> <p>During the meeting, PIP hands over a document drawn up by the company, entitled “development of medical device vigilance incident reports: analyses and interpretations”, which comes to the conclusion that the observed increase in incidents is logical, given their increase in sales, and that the rate of ruptures is comparable to that of its competitors.</p>
31 December 2009:	AFSSAPS requests that PIP provide it with raw data regarding the incidents, and requests further information regarding the analysis presented by PIP on 18 December.
7 January 2010	MHRA emails PIP to chase a response to MHRA’s email of 15 December. PIP respond saying a reply is due shortly.
19 January 2010	An MHRA Breast Implant Group meeting is held which considers a breast implant trend review report carried out the day before. The review notes that there are <i>‘concerns about the longevity of</i>

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	<p><i>PIP silicone implants compared to other manufacturers'</i>. Analysis shows that MHRA's data indicate PIP's mean time to failure is 43 months (compared to 55 and 59 for two other manufacturers) but this work has been '<i>hampered by incomplete data in the [adverse incident tracking system] as it [time to rupture] is not something that we previously recorded routinely.</i>' The BIG meeting notes indicate that work is ongoing to improve the data available for trend review and that the issue of PIP longevity is to be followed up and referred to members of the Committee on the Safety of Devices once the manufacturer has commented.</p>
22 January 2010	<p>MHRA's Clinical Director encourages the Medical Devices Specialist for breast implants to continue to pursue concerns with implant rupture rates with PIP.</p>
22 January 2010	<p>MHRA writes to PIP to raise issues identified in their recent trend review, indicating PIP implants show an increased likelihood of early failures.</p>
22 January 2010	<p>PIP provide AFSSAPS with additional information following AFSSAPS request of 31 December 2009.</p>
25 February 2010	<p>PIP respond to MHRA's letter of 22 January explaining that the increased numbers of implant failures within 4 years of implantation observed by MHRA is actually due to significantly increasing sales experienced a few years previously, with the greater number of implants in use giving rise to a greater number of reported failures. They provide an analysis of sales and adverse incident data to support this assertion.</p>
1 March 2010	<p>Following review of PIP's latest data, AFSSAPS' devices section concludes there are inconsistencies in the information provided and they make an oral request to their inspection section to order an inspection of PIP as soon as possible. They inform the inspection section that PIP breast implants have been connected to a substantial number of ruptures.</p>
16 -18 March 2010	<p>AFSSAPS inspect PIP's manufacturing site, and discover the manufacturer is using an unapproved implant filler on the second</p>

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	day of the inspection (17 March).
18 March 2010	MHRA replies to PIP's response of 25 February regarding the number of failures observed and how this might be related to PIP's sales figures. MHRA questions PIP's interpretation of the figures and ask a number of additional questions to seek information to further explore the concerns they have.
26 March 2010	MHRA asks AFSSAPS for an update on their actions regarding PIP following press report in France about the ' <i>non-conformity of some PIP breast implants and ...subsequent actions being taken by AFSSAPS</i> ' and whether they intend to update other Competent Authorities. AFSSAPS reply saying they are currently carrying out investigations and should be able to provide MHRA with more information on 30 March.
29 March 2010	AFSSAPS recall PIP silicone breast implants and halt their distribution. PIP are notified by an emailed letter from AFSSAPS. A statement is put on the AFSSAPS website.
30 March 2010	PIP forward AFSSAPS email to PIP's UK distributor, Cloverleaf, who email MHRA seeking advice on course of action.
30 March 2010	<p>MHRA emails AFSSAPS for an update on the situation with PIP. AFSSAPS reply saying they decided the day before to recall PIP implants due to concerns over unapproved filler, that they had suspended marketing, distribution, export and use in France of PIP silicone implants, and recalled affected devices. They have issued a press release that morning and are informing surgeons in France. They intend to send an NCAR.</p> <p>AFSSAPS tell MHRA that PIP will go into receivership that evening.</p> <p>AFSSAPS say they will also undertake testing of PIP implants.</p>
30 March 2010	MHRA decides to issue an MDA and alerts PIP's distributor to

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	quarantine stock.
30 March 2010	MHRA writes to BAPRAS informing them of the issues uncovered in France and that implants from PIP will no longer be available.
31 March 2010	<p>MHRA issues Medical Device Alert MDA/2010/025 instructing users to cease implantation of PIP implants and return unused implants to the UK distributor. MHRA also issue a press notice and prepare media handling materials.</p> <p>MHRA informs the European Commission and French authorities of its actions.</p>
31 March 2010	<p>MHRA emails BAPRAS saying they would be grateful for the wider dissemination of information regarding the PIP issue. BAPRAS's representative responds saying highlighting the need to avoid panic and suggests some messages BAPRAS could issue for MHRA's comment.</p>
31 March 2010	MHRA puts a submission to DH Ministers, for information only, informing them of French and UK action.
31 March 2010	<p>MHRA emails AFSSAPS asking for more details regarding which tests the French are planning to carry out and separately seeking more information about the nature of the manufacturing deviation.</p> <p>AFSSAPS reply with information regarding the testing they intend to carry out, stating mechanical testing results will be available within one month and the first biological results in around 6-8 weeks time.</p>
1 April 2010	AFSSAPS reply to MHRA with summary of info from NCAR report which contains further information on the nature of the problem with PIP implants.
1 April 2010	MHRA emails BAAPS and BAPRAS about the need to wait for testing results before MHRA can offer more information to

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	surgeons, but stating that so far there is no evidence of medical harm other than a possible slight increase in the rupture rate.
1 April 2010	AFSSAPS issue a press release stating that rupture of breast implants often requires re-operation. Their advice to surgeons is to stop implanting and call patients for examination. If needed they should prescribe ultrasound examination within 6 months.
1 April 2010	Cloverleaf confirm to MHRA that they have informed Harley Medical Group and Surgicare of the PIP recall of consignment stock.
1-6 April 2010	MHRA confirms with Professor Ian Kimber, toxicology expert on the Committee for the Safety of Devices, that the testing commissioned by France is appropriate.
6 April 2010	MHRA emails AFSSAPS to advise them that MHRA had raised issues around device performance with PIP in recent months and asking if AFSSAPS are in contact with TUV Rheinland. It also asks if AFSSAPS are intending to test any explanted devices and if so whether they would be interested in receiving any explanted devices from UK patients'.
6 April 2010	MHRA emails the Australian regulator, TGA Australia, to update them on the current situation regarding PIP. This email states that <i>'The French are undertaking a series of tests including mechanical tests on the envelope and toxicological tests on the filler and we should have the results of these within the next 4-6 weeks. This is being carried out by a highly reputable laboratory and we felt that there was therefore no need to repeat these.'</i> <i>'We have also indicated to the surgeons that we will not have information for several weeks but that apart from a slightly increased rupture rate, there would not appear to be any clinical issues or problems although obviously we will be issuing further advice immediately we have the toxicological tests and determined the implications of these.'</i>
7 April 2010	The Australian regulator, TGA, reply to MHRA saying their figures for PIP show an acceptable rupture rate of 1-2%. They also state that In 2004, TGA undertook its own conformity assessment. They will be testing samples of PIP implants to see if they match the

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	TGA-approved product from 2004.
7 April 2010	Cloverleaf send MHRA a list of customers who have bought PIP implants since 2000, and advise they are trying to clarify with PIP's liquidator what to do with explanted implants as they are no longer trading and nor are PIP.
7-8 April 2010	MHRA emails AFSSAPS, asking whether PIP directors could be questioned to find out exactly what filler substance was used to 'speed things up'. AFSSAPS reply is non-committal, only confirming which tests will be undertaken.
8-9 April 2010	MHRA asks Cloverleaf for unused implants in case they need to test them. Cloverleaf agrees to provide them.
12-16 April 2010	MHRA emails AFSSAPS asking what information on rupture rates indicated that an audit was necessary, and when test results will be available. AFSSAPS reply saying they're preparing a memo with statistical data which they will send to MHRA along with information on testing ' <i>as soon as possible</i> '.
23 April 2010	AFSSAPS circulate additional info following their NCAR regarding the rupture rates that prompted their inspection of the PIP plant. AFSSAPS report they calculate an incident rate based on the number of incidents reported in a year divided by the number of sales for that year. This showed the 'incident rate was 5 times higher in 2009 than 2007 (0.56% vs. 0.11%)'. PIP's 'incident rate' was also higher than two competitor brands. This triggered the inspection. The inspection also discovered records of a number of ' <i>complaints</i> ' that AFSSAPS were not aware of (i.e. had not been reported to them). Using these additional incident records, AFSSAPS have calculated an even higher incident rate of 9.39% in 2009.
26 April 2010	A letter from the EC to the UK's permanent representative asks for information about what Member States are doing with respect to PIP implants, including informing health professionals and determining where PIP implants were used.

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18 May 2010	MHRA replies to the Medical Devices Directorate in the EC setting out what measures UK has taken regarding PIP implants.
18 May 2010	MHRA learns at a COEN (Compliance and Enforcement Group) meeting in Brussels that French tests may take up to a further 2 months, although mechanical tests might be completed sooner.
28 May 2010	MHRA sends an email to AFSSAPS regarding the availability of the French test results. AFSSAPS respond saying that testing is being delayed due to criminal proceedings and they will update MHRA as soon as possible.
21 June 2010	The British Association of Aesthetic Plastic Surgeons (BAAPS) issues guidance advising women with PIP implants to have an ultrasound in the next 6 months to establish whether there is any weakening or rupture.
23 June 2010	MHRA emails Department of Health Medical Directorate colleagues outlining the issue with PIP implants, pointing out the potential NHS resource implications and public health implications depending on the results of toxicology testing, and asking who else in DH should be alerted ahead of a further submission to Ministers.
21-24 June 2010	MHRA emails AFSSAPS twice for an update on French test results and asking for information on PIP's insurer due to queries regarding compensation claims.
30 June 2010	At an EU vigilance Medical Devices Expert Group (MDEG) meeting, AFSSAPS provide a revised timetable for test results due to the French courts impounding PIP stock – results are expected by the end of July except for genotoxicity, which will be the end of August.
1 July 2010	MHRA considers the revised timetable for French tests following Vigilance MDEG meeting.

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2 July 2010	A note of the NBOG (Notified Body Operations Group) meeting of 1 July is circulated. Under the item on PIP: the notes state that <i>'The French gave a presentation in to the background regarding these products. A 2 man team from Afssaps had been in at the manufacturing plant for 7 days when one of the inspectors noted an employee peeling off a label from a bulk container of raw material as they approached. On investigation it was identified to be a different grade of silicone than that which was expected to be available. A thorough review of the paperwork was then followed through where it was found that there was in place a deliberate company wide cover up. All the documentation and records indicated that the correct grade of silicone was being used. Samples for external independent testing were manufactured using the correct grade of silicone.'</i>
1-2 July 2010	MHRA asks Professor Ian Kimber for help in identifying a way to conduct UK testing of PIP implants (specifically genotoxicity) given the delays in French results.
5 July 2010	MHRA consults independent genotoxicity expert Professor David Kirkland on the issue of testing PIP implant toxicity.
5 July 2010	MHRA officials ask if their Chief Executive or Director could speak to the Director General of AFSSAPS, Jean Marimbert, to establish whether the French tests are being carried out. They are informed that the MHRA Chief Executive, Kent Woods and AFSSAPS Director General have discussed it, that the French courts had impounded the PIP implants and that Jean Marimbert will be writing to the MHRA to outline the timetable for tests.
6 July 2010	MHRA formally commissions UK testing of PIP implants.
6 – 9 July 2010	MHRA consult DH on potential handling implications of toxicology tests, to inform their advice to Ministers.
9 July 2010	Jean Marimbert, Director General of AFSSAPS, writes to Kent Woods. Due to French court proceedings, their tests did not begin until the second half of June. The first results are expected end July, some mid August and some the end August. Global analysis

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	won't be available until mid September.
9 July 2010	MHRA informs BAPRAS, Independent Healthcare Advisory Services (IHAS) and Harley Medical Group that the French test results will be delayed to mid September.
13 -14 July 2010	The Director General of AFSSAPS asks the MHRA Chief Executive to confirm reports that MHRA has commissioned its own tests due to French test delays. MHRA Chief Executive replies to confirm, saying the UK tests are less extensive than those AFSSAPS are undertaking, and that he will share the results, which are due in mid August.
16 July 2010	Submission sent from MHRA to DH Ministers for information. This submission provides an update on the actions and investigations being undertaken by MHRA and the French authorities, including the delays to the French tests and the tests commissioned by the MHRA.
20 July 2010	Earl Howe responds noting MHRA submission of 16 July
22 July 2010	MHRA writes to AFSSAPS complaining that they were not informed more quickly of the delays to the French tests and have now commissioned more limited tests of their own to give a quicker indication of potential safety issues.
26 July 2010	MHRA receive the first batch of preliminary results from their tests which suggest no evidence for mutagenicity/toxicity so far.
26 July 2010	AFSSAPS responds to the MHRA's email of 22 July apologising that they were not updated regarding delays to the tests, and separately circulates a link to English translations of its update and Q&A on its website, including when their test results will be available.
27 July 2010	AFSSAPS emails all European Competent Authorities asking whether they have commissioned their own tests, and if so to

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	share the results.
12 August 2010	MHRA receives the second batch of preliminary results of their tests, indicating a negative (no mutagenicity) result.
17 -20 August 2010	The MHRA informs AFSSAPS and, separately, Martin Lee (ABS) that the initial UK results indicate no toxicity. MHRA is holding an internal teleconference to which he and Professor Simon Kay (BAPRAS) are invited.
19 August 2010	Submission from MHRA to DH Ministers on preliminary results of its testing, reporting no genotoxicity or chemical toxicity of filler material.
20 August 2010	AFSSAPS sends MHRA initial results of two of their tests. MHRA speaks to AFSSAPS about what tests UK is carrying out. MHRA emails ABS and BAPRAS concerning preliminary French results that suggest the implant shells are non-compliant and that there is a lack of clarity around toxicity and irritability results.
20-24 August 2010	MHRA officials and Professor Ian Kimber discuss the results of the PIP implant toxicology tests, both the UK results and comparison with French results.
23 August 2010	MHRA CE emails the AFSSAPS Director General with UK test results.
26 August 2010	Meeting held at MHRA with professional body representation (BAPRAS, ABS), to consider analysis of test results and course of action.  MHRA holds teleconference with AFSSAPS later that day.
26 August 2010	Earl Howe notes MHRA's submission of 18 August 2010.

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27 August 2010	MHRA Clinical Director for Devices emails Professor Simon Kay and Lee Martin (ABS) following the meeting of 26 August, updating on the teleconference held with AFSSAPS, which covered the French results, and outlining plan to inform Ministers in the next week before going public. She highlights the need to coordinate advice on BAPRAS and ABS websites.
28 August 2010	Earl Howe responds noting MHRA submission of 19 August.
28 August – 1 September 2010	<p>MHRA officials and Professor David Kirkland discuss the UK and French silicone filler toxicity testing by telephone and email. These discussions conclude the UK-commissioned ‘Ames’ test results (using bacteria to determine how mutagenic a chemical is) are encouraging and consistent with the French Ames testing. The French ‘micronucleus’ testing (which uses mice to test how genotoxic or carcinogenic a chemical is) probably indicates there is not a problem, but an in vitro micronucleus test may need to be carried out as this can be more sensitive and accurate. In order to assess this properly however, the experts require more information on how the French conducted their tests.</p> <p>MHRA’s Clinical Director for Devices confirms that Professor Ian Kimber broadly agrees with Professor Kirkland’s assessment and Professor Kimber further confirms these results don’t change the current UK position.</p> <p>Given the uncertainties around the micronucleus testing, there are internal MHRA discussions around the possible need to commission an in vitro micronucleus assay. The results so far suggest no evidence of mutagenic activity so the in vitro test may not be necessary however. Officials therefore advise awaiting a few days for further information from France before commissioning any more tests.</p>
1 September 2010	Submission from MHRA to DH Ministers informing them of full testing results and discussion with members of the Committee on the Safety of Devices. These have concluded that there is no evidence of any associated risk with filler material. The submission seeks agreement to make an announcement on the basis of these results.

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2 September 2010	Earl Howe responds agreeing recommendations in MHRA submission of 1 September.
3 September 2010	MHRA Clinical Director for Devices shares MHRA press statement with IHAS, Harley Medical Group and Professor David Sharpe, outlining that the UK results do not suggest any toxicity of silicone filler, and that further results will follow from the French tests
3 September 2010	MHRA puts UK test results on its website, reporting 'encouraging' results that show no genotoxicity and no chemical toxicity. The MHRA statement includes a link to advice on the ABS and BAPRAS websites.
14 & 20 September 2010	<p>AFSSAPS emails MHRA to say the French test results will be available on 17 Sept, and will be published on 21 Sept after consultation with experts, clinicians etc. They will inform MHRA before 21<sup>st</sup> of their decision on whether further tests will be required.</p> <p>AFSSAPS later emails MHRA to inform them that the press conference on test results has been pushed back to 28 September.</p>
14 & 20 September 2010	MHRA emails Australian competent authority asking for results of any tests they have carried out on PIP implants.
27 – 28 September 2010	<p>MHRA receives an email and embargoed press notice from AFSSAPS regarding the further results and analysis of the French testing, ahead of AFSSAPS publishing the press notice and holding a press conference the following morning. The results show no evidence of genotoxicity or chemical toxicity, but mechanical testing suggests may be an increased risk of rupture.</p> <p>One of the genotoxicity tests was however, inconclusive and further testing is to be conducted by early 2011. [AFSSAPS publishes these results in April 2011]. AFSSAPS also report that <i>'The results of the intradermal irritation test show an irritant</i></p>

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	<p><i>behaviour of PIP gel...'</i></p> <p>On this basis AFSSAPS will be recommending ultrasound of all PIP implanted patients within 6 months and explantation of any implants subsequently found to rupture.</p> <p>MHRA summarises French tests and MHRA conclusions on its website via a press release.</p>
28 September 2010	<p>MHRA asks Professor Simon Kay, Lee Martin and Martin Lee for clinical advice following receipt of the full test results and analysis from AFSSAPS and noting the potential for irritation and AFSSAPS' recommendation for routine ultrasound.</p> <p>Professor Kay advises; <i>"At present my feeling is there is still no hard scientific reason to investigate or explant these devices, but equally they are acknowledged as defective and the potential harm is probably not firmly known, especially we need to understand how useful in predicting the eventual consequences of gel exposure are the current test results: after all the potential for harm at 10 years or more is what will be seen to matter."</i></p> <p>He warns however that the French recommendation for routine ultrasound may lead to the perception that the UK's response is not adequate and increase the pressure on the UK regardless of the scientific position.</p>
29 September 2010	<p>The Australian regulator (TGA) replies to MHRA regarding tests it has carried out on PIP implants. Their cytotoxicity tests on the gel and shell were negative. The implants passed tests on tensile properties of the implant shell. Their results are not consistent with French test results.</p> <p>MHRA shares these results with Professor Kay, Lee Martin and Martin Lee.</p>
29 September 2010	<p>Martin Lee responds to MHRA saying looking at the French and Australian information, he does not see an immediate need to change ABS's current advice</p>

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29 September 2010	MHRA informs IHAS and BAAPS of conclusions from latest MHRA, French and Australian test results, and MHRA's proposed next steps including advising there is no need for routine ultrasound or explants and that updated information will be placed on MHRA's website on 30 September.
29 September 2010	BAAPS issue statement highlighting possible dangers of PIP implants following the French test results, and recommending ultrasound within 6 months and removal of both implants if there is any evidence of weakness or rupture.
29 September 2010	TGA circulates feedback received to the US Food and Drug Administration's NCAR on ALCL. None of the responding authorities had received reports of ALCL or Non-Hodgkins Lymphoma associated with breast implants. The British Association of Oncologists had no knowledge of any ALCL reports in breast implant patients.
30 September 2010	MHRA's Clinical Director for Devices emails TGA regarding the MHRA's intended Medical Device Alert and advice. TGA reply that they intend to issue a similar statement, <i>'except we are unlikely to give much weight to notion of early rupture being a possible problem... This is based on our tensile test results and the low numbers of reports we have had for this implant, despite the publicity given to the issue.'</i>
30 September 2010	MHRA places an updated statement on its website saying the French results of 27 September support earlier UK results in indicating no toxicity, as have similar results from TGA.
4 October 2010	MHRA issues Medical Device Alert MDA/2010/078 providing advice on clinical management of women implanted with PIP implants. This advises UK clinicians to contact women with PIP implants and to reassure them that there is currently no evidence of any health risk associated with filler and no indication for any routine action in the form of explanation or ultrasound.
6 October 2010	Submission from MHRA to DH Ministers for information, informing them of the full results of French testing and AFSSAPS'

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	<p>recommendation that women receive ultrasound within 6 months. MHRA has concluded there is “<i>no evidence of abnormal health risks</i>” and “<i>no indication for any routine action</i>”.</p>
11 October 2010	<p>Earl Howe responds to MHRA submission of 6 October, asking why the UK advice differs from that given in France and requesting a more detailed note including findings on risk of mechanical rupture.</p>
12-13 October 2010	<p>AFSSAPS and MHRA hold a couple of teleconferences to discuss French concerns that surgeons in the UK are less concerned than those in France about possible ruptures or gel leakage and to allow AFSSAPS to discuss PIP implants with UK experts.</p>
12 October 2010	<p>MHRA’s Clinical Director for Devices reports via internal email that Professor Kimber feels there is no cause for concern about developmental effects of PIP implant filler. However, the risks around breast feeding (prompted by French test results suggesting risk of gel ‘leaching’) are more difficult to assess in the absence of information on the possible disposition of implant materials following leaks.</p>
13 October 2010	<p>MHRA’s Clinical Director for Devices responds to Earl Howe’s queries from 11 October. She explains MHRA’s advice has been consistent with the French except for the fact that the MHRA is not advocating routine ultrasound. This is based on expert advice. On ruptures, the French results are not consistent with Australian tests which showed no increased risk of rupture. On the advice of expert surgeons UK advice on ruptures is the same as for implants in general – ie removal if the gel is causing problems or if patient is concerned.</p>
19 October 2010	<p>MHRA Clinical Director for Devices emails the National Clinical Director for Imaging, Dr Erika Denton, highlighting the French proposal to use routine ultrasound, that the MHRA view is that this is inappropriate, and asking what the best imaging technique is for detecting implant rupture. Dr Denton replies it is MRI.</p>
25 October 2010	<p>Earl Howe responds noting the MHRA’s further advice of 13</p>

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	October.
25-26 October 2010	MHRA's Clinical Director for Devices seeks further advice from Professor Ian Kimber about the potential risks to breast feeding mothers due to French test results suggesting 'increased leaching' from PIP implants. Professor Kimber suggests there are no new grounds for concern but that there may be some work needed to substantiate that view and asks if the MHRA has considered establishing a group.
10 November 2010	MHRA Clinical Director for Devices emails press lines concerning the use of ultrasound to colleagues and external experts: <i>'Discussions have been held with Dr Erika Denton, Consultant Radiologist, National Clinical Director for Imaging, Department of Health on the question of Radiology of the Breast and PIP Implants. Her advice is that routine ultrasound is not indicated since it is not evidence-based. She supports the view that all implanted women who are concerned about their breasts or think that their implants may have ruptured, should seek clinical advice from the implanting surgeon who will, as indicated, refer them for breast radiology according to local protocol.'</i>
26 January 2011	FDA issues Medical Device Safety Communication – Reports of Anaplastic Large Cell Lymphoma in Women with Breast Implants.  MHRA prepares press lines: <i>"The MHRA recently reviewed available evidence for association of cancers for women with breast implants in consultation with the relevant professional bodies for breast surgery and surgical oncology and concluded that there was insufficient evidence to indicate any association with cancer. Additionally MHRA worked with the Cancer Registry and could find no evidence for any association."</i>  The MHRA has not received any reports of women with breast implants of any type in the UK with a diagnosis of ALCL."
27 January 2011	MHRA Clinical Director for Devices seeks advice from the National Clinical Director for Imaging regarding the FDA recommendation that women with breast implants have MRI scans every 3 years, asking if she thinks there is merit in screening like this in the NHS. Dr Denton replies this would be

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	inappropriate.
1 February 2011	MHRA's Clinical Director for Devices consults Professor Simon Kay concerning the FDA's ALCL issue.
1 -2 February 2011	MHRA officials meet Professor Lucas at UCL Institute of Child Health to discuss the possible risks to breastfeeding. They agreed the first step is to conduct a literature review and put advice on MHRA website as soon as possible, without setting up an Expert Group unless the literature review indicates evidence of risk to safety.
14-15 February 2011	Literature search on breast feeding has been completed. MHRA's Clinical Director indicates there is no cause for concern. MHRA officials coordinate putting advice on website and in their breast implant leaflet.
16 February 2011	<p>MHRA issues Medical Device Alert MDA/2011/017 regarding FDA's communication [of 26 Jan 2011] saying <i>'there is uncertain evidence that women with breast implants may have a very small but increased risk of anaplastic large cell lymphoma (ALCL) of the breast'</i>. <i>'No change to current best practice is needed.'</i></p> <p>Surgeons are encouraged to report any adverse incidents to the MHRA. Women should be encouraged to self-examine and seek medical advice if concerned.</p>
25 February 2011	Internal MHRA email – final AFSSAPS tests have been delayed due to a fire at the laboratory. Results now expected late March.
10 March 2011	MHRA report on internal literature review on breast implants and breast feeding – indicates no cause for concern
15 March 2011	Clinical Director for Devices emails web team with changes to breast implant pages on MHRA website to make it easier to navigate for professionals and users.

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31 March 2011	AFSSAPS tell MHRA that the latest French test results show there to be no problem with PIP implants and they will send them the results soon.
4 April 2011	MHRA Clinical Director for Devices emails colleagues regarding the French test results – they should await the formal report then update website and inform the professional bodies.
14 April 2011	AFSSAPS post PIP breast implants update on their website and circulate the information to CAs, saying there are no genotoxic effects for the PIP silicone gel filler material. AFSSAPS recommend ultrasound every 6 months and explantation of ruptured implants or suspected ruptured implants.
21 April 2011	<p>MHRA issues updated advice on its website stating that that <i>“Our advice continues to be that women who are concerned... should seek clinical advice from the implanting surgeon.”</i></p> <p>MHRA internal emails also indicate they are formally notifying relevant professional organisations.</p> <p>MHRA issues a press statement stating that the French regulator confirms <i>no evidence of genotoxicity (potential for cancer) or chemical toxicity of the filler material inside the devices.</i></p>
April 2011	MHRA publishes an updated breast implant information leaflet with advice for women considering breast implants.
29 June 2011	AFFSAPS publishes English translation of its tests summary on its website.
24 November 2011	AFFSAPPS inform all other competent authorities of the press reports regarding the death of a French PIP breast implant patient who developed lymphoma. MHRA begins internal consideration of the implications.

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25 November 2011	Internal MHRA emails set out data on adverse incidents reported to MHRA since 2009 – approximately 300 (104 in 2009, 110 in 2010, 92 in 2011 to November). No reported incidents where lymphoma confirmed to be in association with a PIP breast implant. Reactive press lines are prepared saying <i>‘there is insufficient evidence to indicate any association with cancer’</i> . Advice continues to be that <i>‘Women who are concerned...should seek clinical advice from their implanting surgeon.’</i>
1 December 2011	Harley Medical emails MHRA asking if they have any comments regarding the recent reports into ALCL in a woman with a PIP implant. MHRA responds giving its press lines.
5 December 2011	The French General Directorate of Health asks the French National Cancer Institute (INCa) to set up an expert group to ‘recommend the strategy to be adopted by health professionals’.
6 December 2011	AFSSAPS writes to competent authorities informing them of the death of a woman with PIP implants from ALCL in France, citing FDA data on a possible link, and asking each CA to provide any information they have on adverse effects reported in their country for breast implants, in particular PIP, reports of ALCL and possible link to breast implants etc. AFSSAPS asks for the information as soon as possible. The letter includes an information update that is on the AFSSAPS website on the issue. Information sheet that was put on AFSSAPS website includes: AFSSAPS recommends that patients contact their surgeon to discuss the possibility of explantation even without clinical signs of deterioration of the prosthesis.’ <i>‘All women with PIP breast implants will be reimbursed for their medical and surgical expenses related to explantation’; ‘women who are recovering from a reconstruction after breast cancer surgery will also be reimbursed for the implantation of a new prosthesis.’</i>
6 December 2011	Emails from the Birkdale Clinic to MHRA highlighting recent reports of lymphoma and asking how to respond to concerned patients.
6 December 2011	Following the email from the Birkdale Clinic regarding the reports of possible links between lymphoma and PIP breast implants, MHRA officials discuss putting MHRA’s position on the MHRA

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	<p>website. One advises against, as to do so may “create a false impression of level of significance leading the public to conclude that there was a link”.</p>
7 December 2011	<p>French Ministry of Health establishes a ‘monitoring’ committee on PIP implants.</p>
12 December 2011	<p>MHRA’s Clinical Director for Devices emails colleagues – AFSSAPS have no new ALCL cases.</p>
12 December 2011	<p>Harley Medical email MHRA to see if they intend to issue advice around investigation and possible explantation as France has done, following 2<sup>nd</sup> case of ALCL. MHRA reply saying they are in contact with AFSSAPS and are awaiting findings of their investigation to see if any further action is required.</p>
14 December 2011	<p>The French Health Ministry’s monitoring committee meets for the first time.</p> <p>AFSSAPS establishes its own internal supervisory committee.</p>
16 December 2011	<p>MHRA’s Clinical Director for Devices emails colleagues – no evidence to suggest their advice should change. She has emailed AFSSAPS for more information on their ALCL case.</p>
16 December 2011	<p>MHRA’s Clinical Director for Devices emails AFSSAPS seeking confirmation of the cancer case in France. AFSSAPS respond confirming the case of ALCL, saying they have updated the information on their website and asking for a response to their letter of 6 December.</p>
20 December 2011	<p>MHRA emails AFSSAPS regarding French press reports that the French Director-General of Health is stating that all women with PIP implants should have them removed and asking whether France has changed its advice. AFSSAPS replies that no decision has yet been taken. The Health Director General has gone on radio to explain that, and that there is no change to the French</p>

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	recommendations of 6 December 2011.
20 December 2011	<p>AFFSAPS contacts all European competent authorities, giving background to the French press reports regarding routine explantation and stating that they are waiting for the Ministry of Health's decision on explantation. The French National Cancer Institute's expert group is expected to give advice on 23 December.</p> <p>MHRA prepares press lines saying it is aware of the recent report in France of the death of a woman implanted with PIP breast implants from ALCL. MHRA will continue to monitor for any associations with all implants. It will continue to liaise with AFSSAPS and consider any new evidence as a priority. MHRA advice to women with PIP implants remains unchanged, that they should seek advice from their implanting surgeon and that there is no evidence to support routine removal of PIP or any other silicone gel breast implant.</p>
20 December 2011	MHRA press office updates Department of Health private offices regarding French press coverage, the French Health Minister's statement on French radio that no decision had been taken on explantation yet, MHRA's latest lines and UK press interest.
21 December 2011	MHRA sends AFSSAPS UK rupture data in response to their letter of 6 December.
21 December 2011	Note from MHRA to Ministers on PIP issues, including actions MHRA has taken to establish the safety of PIP implants, and what has triggered the resurgence of interest in the issue.
21 December 2011	MHRA's Clinical Director for Devices emails DH private offices with an update following a European Commission teleconference. Accompanying press lines advise against routine explantation in the UK, and state that there is no evidence that PIP rupture rates are abnormally high.
21 December 2011	An EC Health Security Committee teleconference is held on 21 December to discuss the PIP implant issue at the request of

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	France. French representatives outline the concerns they have, including any possible link to cancer, and that a decision on explantation would be made on 23 December.
21 December 2011	MHRA circulates a briefing note to DH, MHRA, UK Health Departments and others outlining the discussion held by teleconference with other EU countries on PIP, noting it sounded likely that France would announce on 23 December that it is recommending routine explantation. MHRA has discussions with other health regulatory experts from France, Netherlands, Portugal, Italy, Ireland, Hungary, Austria, Denmark and Malta. All agree no evidence of increased incidence of cancer associated with PIP implants and no evidence of disproportionate rupture rates other than in France. Information obtained from Australian regulator (TGA) is consistent with rupture figures from all above countries except France.
21 December 2011	MHRA issues a statement on press reports speculating imminent French government announcement. AFSSAPS has confirmed that it will issue a statement on 23 December but has not indicated what advice will be given in relation to patient health and the need to remove implants.
21 December 2011	MHRA's Clinical Director for Devices invites surgeons Tim Goodacre, Richard Rainsbury, Simon Kay, Lee Martin and Martin Lee to be on an Expert Advisory Group to consider all available data, and provides them with MHRA's latest position with respect to the probable French announcement.
21 December 2011	MHRA's Clinical Director for Devices emails private providers Spire and Harley Medical with MHRA's latest press lines.
22 December 2011	AFSSAPS officials take part in the meeting of INCa's expert group.
22 December 2011	The NHS Chief Executive's office ask MHRA when the Expert Advisory Group will be in a position to advise, as they are concerned about the UK position should the French government recommend routine explantation. MHRA responds advising it is likely the French government will recommend routine explantation but that their impression from the EC teleconference was that it

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	was unlikely any other country would follow suit. The lack of new evidence to support routine explantation would mean support from UK professional bodies for the UK to hold its position on not recommending explantation.
22 December 2011	MHRA's Clinical Director for Devices emails private providers Transform, Spire and Harley Medical about the latest press lines and plans for reacting to the anticipated French announcement.
22 December 2011	MHRA emails DH private offices with a further update following the EC teleconference, saying it is likely the French will announce routine explantation and attaching press lines that say the UK is not changing its advice. Advice emphasises that there were no claims from any member states, including France, that they had new evidence concerning a causal link between cancer and breast implants.
22 December 2011	MHRA emails DH private offices following a conversation with AFSSAPS. AFSSAPS are likely to recommend explantation, the French government will pay for this, it is not supported by new evidence, and they will announce this at about 10:30 on 23 December. MHRA alerts BAPRAS, ABS, BAAPS, and Professor Ian Kimber to key points and press lines.
22 December 2011	MHRA considers TGA's PIP data and advice that was put on TGA website on 21 December. It is consistent with the reported UK rupture rate of around 1%.
22 December 2011	Secretary of State for Health speaks to French Minister of Health regarding the imminent French recommendation for precautionary routine explantation of implants.
23 December 2011	French Ministry of Health announces its recommendation that all women with PIP implants should have them removed, on a preventative / non-emergency basis. It states that there is no increased risk of cancer – the risk comes from ruptures which may lead to inflammatory reactions.

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23 December 2011	INCa's advice is published, stating that there is no evidence of a link to cancer with PIP implants and that "There is currently no justification for an urgent removal of these implants...in the absence of any symptoms, it is recommended that the recommendations of AFSSAPS be followed for monitoring patients, i.e. a clinical and ultrasound examination every six months".
23 December 2011	MHRA asks BAPRAS, ABS, and BAAPS for estimation of the risks of explantation. BAAPS responds with a description of how PIP implants are defective as compared with others and that where immediate problems are experienced they should be removed, then respond further saying risk of explantation is no greater than for implantation, including a 0.5% infection rate. ABS responds with a similar assessment (ie risk of explantation approximates that of implantation) and that infection/haematoma risk is about 1%.
23 December 2011	MHRA Clinical Director for Devices emails Transform, Spire, Harley Medical, BUPA and IHAS about the French announcement and MHRA's position. Transform responds indicating a large volume of contacts have come in from concerned women.
23 December 2011	TGA email MHRA asking for information and whether they intend to change their advice to patients as TGA have similar rates of failure/rupture to MHRA. MHRA share background briefing.
23 December 2011	MHRA issues press statement – not recommending routine removal of PIP silicone gel breast implants in the UK; no evidence of increase in incidents of cancer; no evidence of disproportionate rupture rates other than in France.
23 December 2011	MHRA emails DH private offices with an update following a further EC teleconference after the French announcement. France have not provided evidence supporting their action and other EC states have indicated they would not be following the French lead.
23 December 2011	DH Chief Medical Officer writes to GPs, NHS Medical Directors and Plastic Surgeons relaying MHRA advice and linking to MHRA

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	press statement.
24 December 2011	Cut off date for review

## 2. The European system for medical device regulation

The various regulatory systems in respect of medical devices then existing in the member states of the European Union, began to be replaced in January 1993 when the first European Directives regulating the marketing of medical devices started to come into effect. The underlying objective of these Directives was to remove technical barriers to trade by providing manufacturers with a single set of regulatory requirements that, once met, would provide free and unhindered access to the EU market. At the same time the Directives aimed at providing users and patients of medical devices a high level of confidence that devices, when used in accordance with the manufacturer's instructions, were safe and would perform as claimed.

The manufacturer affixes medical devices meeting the requirements laid out in the relevant Directive(s) with the CE mark.

The medical device Directives that have been agreed and put into national law so far are:

- the Active Implantable Medical Devices Directive (AIMDD) which came fully into force in January 1995 and covers powered implants (such as pacemakers) or partial implants which are left in the body.
- the Medical Devices Directive (MDD) which came fully into force in June 1998 and covers a broad range of products from sticking plasters to X-ray machines including breast implants.
- the In Vitro Diagnostic (IVD) Medical Devices Directive which covers test kits and instruments used in vitro for examining specimens taken from the human body (eg blood grouping reagents, pregnancy and Hepatitis B test kits). This Directive came into force in June 2000.
- the medical devices incorporating stable derivatives of human blood or human plasma Directives. These came into effect in June 2002 and cover the inclusion of materials such as albumin, thrombin, fibrinogen and immunoglobulins in devices such as stents, leads, heart valves, vascular grafts, catheters, filters and haemostats.
- the Directive re-classifying breast implants as class III medical devices.
- the Directive as regards medical devices manufactured utilising tissues of animal origin;
- the Directive revising the AIMDD and the MDD which came into force in March 2010, and which among other issues clarified the requirements for clinical data and re-classification of a number of products; and
- the Directive re-classifying total joint replacements as class III medical devices.

## Key features of the Directives

- The Directives require the competent authority (CA) in each member state to ensure effective implementation. In the UK, the competent authority is the Secretary of State for Health acting through the MHRA. The main responsibilities of the CA, which for devices, have not been devolved in anyway to the Devolved Administrations, involve:
  - enforcing compliance with the implementing regulations;
  - registration of manufacturers of primarily low risk devices;
  - assessing notifications for clinical investigations;
  - monitoring and designating the notified bodies who assess the conformity of certain classes of devices with the regulatory requirements set out in the various Directives; and
  - authorising the use of non-CE marked medical devices on humanitarian grounds.
- All the Directives establish a list of essential requirements which devices must meet before being placed on the market, as well as imposing various other regulatory requirements upon the manufacturer. The essential requirements concern matters such as the safety and performance of the device and the amount and type of information given to the user of the device by way of the label or instructions for use.
- The Directives set out various options which the manufacturer may choose to demonstrate compliance. These will involve, broadly, either an assessment of the manufacturer's quality control systems, manufacturing processes, or individual testing of each device type. The aim is to match the level of control of the device – and thus the depth and challenge of the conformity assessment procedure adopted - to the perceived risk associated with the product. In the MDD, this is achieved by a classification system whereby devices are grouped into one of three classes according to a series of rules. Class I covers products generally regarded as low risk such as spectacles, bandages and non-invasive products. Manufacturers of these devices are required to check for themselves that they comply with the Directive, make a declaration to this effect and register their details with the Competent Authority. For medium risk products (Class II a and b), eg contraceptive devices, contact lens care products and for higher risk products (Class III), eg intra-uterine contraceptive devices, devices combined with a medicinal product and breast implants, compliance with the Directive must be independently assessed by a Notified Body. These are independent third party certification organisations designated by the Competent Authority to carry out the conformity assessment procedures stipulated in the annexes to the Directives. Only when the Notified Body certifies that the manufacturing processes or the products meet the requirements may the manufacturer CE mark the device and place it on the market.

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- The Directives establish a vigilance system whereby the manufacturer must report to the CA all serious adverse incidents for evaluation. If appropriate details are also reported to other member states and the Commission in order to prevent similar incidents occurring elsewhere in the Community.

The MHRA has a statutory responsibility to ensure manufacturers comply with the Regulations. It does this by investigating all allegations of non-compliance received as well as operating its own pro-active programme. Where investigation proves the device does not conform to the regulatory requirements, action can be taken to remove the offending device from the market. However in practice unless the problem represents a serious safety matter, the CA and the manufacturer usually will work together to correct the fault amicably in adherence to the Hampton principles.

Member states also have the power to withdraw from the market any product that it considers is a danger to public health. This is termed the "safeguard clause" and is common to other single market measures.

# Endnotes

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<sup>i</sup> Hydrogel was a type of breast implant filler used by PIP until December 2000, when PIP voluntarily withdrew their hydrogel implants from sale due to concerns about a lack of testing information regarding the safety of Hydrogel as an implant filler. The Review team considered the fact that the MHRA's interactions with PIP concerning silicone implants were undertaken in the context of other problems with another type of PIP implant. However in this instance the MHRA's predecessor the Medical Devices Agency had correctly identified that there were inadequacies in PIP's biological safety assessment of their Hydrogel filler, due to a lack of long-term toxicity data or clinical follow-up, plus some methodological flaws in their pre-clinical tests. When presented with these concerns PIP agreed as a precautionary measure to voluntarily withdraw these implants from the UK market until the MDA's concerns could be addressed. While the lack of satisfactory safety data may suggest the MHRA should have had wider concerns about PIP's practices, their willingness to voluntarily withdraw their product suggested an appropriate level of cooperation with the Regulator. It is therefore not unreasonable for the MHRA to have continued its interactions with PIP on the assumption that the manufacturer was acting in good faith. For this reason, the Review team considers the issues with hydrogel implants to be peripheral to the issues with PIP silicone implants.

<sup>ii</sup> Source – MHRA

<sup>iii</sup> Available at <http://cr.rsmjournals.com/content/17/2/43.abstract>

<sup>iv</sup> French version available at <http://www.ladocumentationfrancaise.fr/var/storage/rapports-publics//124000077/0000.pdf>

<sup>v</sup> *“un groupe d'experts qui doit recommander la conduite à tenir par les professionnels de santé”*

<sup>vi</sup> *“Il n'existe pas d'argument à ce jour justifiant une explantation en urgence mais le groupe d'experts a rappelé le risque de rupture prématurée et les incertitudes concernant les complications liées au caractère irritant de ce gel. En l'absence de tout symptôme, il est rappelé pour le suivi des patientes, les recommandations de l'AFSSAPS, à savoir un examen clinique et une échographie tous les six mois, en ciblant pour chacun de ces examens les seins et les zones ganglionnaires axillaires. En cas de signe anormal, une consultation spécialisée est préconisée pour une prise en charge.”*

<sup>vii</sup> Available at [http://www.sante.gouv.fr/IMG/pdf/Synthese\\_Rapport\\_PIP\\_def\\_01\\_02\\_12.pdf](http://www.sante.gouv.fr/IMG/pdf/Synthese_Rapport_PIP_def_01_02_12.pdf)

<sup>viii</sup> *“Dans les suites de ce premier comité de suivi et après avoir pris connaissance de l'avis des experts réunis par l'INCa, le ministre du travail, de l'emploi et de la santé et la secrétaire d'Etat à la santé déclarent qu'ils souhaitent que l'explantation de prothèses, même sans signe clinique de détérioration de l'implant, soit systématiquement proposée aux femmes au cours d'un entretien avec leur chirurgien.”*

<sup>ix</sup> Available at <http://www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON076499>  
<http://www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON096755>  
<http://www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON108774>

<sup>x</sup> Available at <http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON076513>  
<http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON093706>  
<http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON094170>  
<http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON114614>  
<http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON137935>