
MEDICAL DEVICES: Guidance document

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**GUIDELINES FOR CONFORMITY ASSESSMENT
OF BREAST IMPLANTS ACCORDING TO
DIRECTIVE 93/42/EEC RELATING TO MEDICAL DEVICES**

These guidelines aim at promoting a common approach by the manufacturers of breast implants, the Notified Bodies involved in the conformity assessment procedures according to the relevant annexes of the MDD and by the Competent Authorities charged with safeguarding Public Health.

They have been carefully drafted through a process of consultation with various interested parties during which intermediate drafts were circulated and comments were taken up in the document. Therefore, this document reflects positions taken in particular by representatives of Competent Authorities and Commission Services, Notified Bodies, industry and other interested parties in the medical devices sector.

These guidelines are not legally binding. It is recognised that under given circumstances, for example, as a result of scientific developments, an alternative approach may be possible or appropriate to comply with the legal requirements.

Due to the participation of the aforementioned interested parties and of experts from Competent Authorities, it is anticipated that these guidelines will be followed within the Member States and, therefore, ensure uniform application of relevant Directive provisions.

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1. INTRODUCTION

Breast implants are usually Class IIb products, in some cases they are class III according to MDD, Annex IX, Rules 8, 13 or 17.

The product related hazards of breast implants can be divided into the following categories:

- hazards associated with the design and manufacture of the device (see 2.1, 2.2, 2.3 and 2.4)
- hazards associated with the surgery and inherent hazards associated with the clinical use of breast implants (see 2.5).

In the following table, the hazards and the related guidelines are listed.

The manufacturer must evaluate the risk associated with each hazard listed below. The second column of the table gives the corresponding guidelines to be considered.

The information is not exhaustive.

This information can be considered as one of the basis for the risk analysis which must be performed.

2. GUIDELINES

2.1 Table of hazards associated with the design and manufacture of the device with the related Guidelines.

Hazards	Guidelines
Mechanical failure	Results of mechanical testing according to pr EN 12180, 7.1 and adequate quality control at the relevant steps of manufacture must be available. With regard to the test of abrasion, the manufacturer should address these related hazards even for implants filled with silicone gel and estimate the corresponding risk. He should describe the test used and justify it
Rupture after implantation	To be addressed in the clinical evaluation
Capsular contraction	To be addressed in the clinical evaluation
Other local complications	To be addressed in the clinical evaluation
Lack of sterility of the product	The product must be provided sterile. The EN 550 series of standards can be used where appropriate. The sterilisation process must have been validated adequately and documented in the technical file. The validation must demonstrate the fulfilment of EN 556.

Lack of biocompatibility	<p>Biological evaluation can be performed according to prEN 14630 and prEN 12180, 6 and 7.1.7 in combination with EN 30993-1, ISO/DIS 14538, and EN 1441, annex B.</p> <p>Evaluation of biocompatibility should cover the shell, the filling material and the bleed materials as well as all other materials which could be in contact with the tissues in case of rupture of the envelope, as identified in the risk analysis.</p> <p>All identified hazards should be addressed.</p> <p>In particular, all the following hazards should be object of the appropriate in-vitro tests or animals studies, unless a justification is given for not performing them. In vitro tests could also be used to assess propensity to induce the release of pro-inflammatory cytokines.</p> <ul style="list-style-type: none"> - <u>Envelope</u> : cytotoxicity, haemocompatibility (haemolysis, {activation of complement}), genotoxicity, carcinogenicity . - <u>Filling material</u> : cytotoxicity, systemic toxicity, intradermal irritation, sensitisation , genotoxicity, carcinogenicity, haemocompatibility (hemolysis, activation of coagulation, platelet activation, {activation of complement}), - <u>End product</u>: cytotoxicity, systemic toxicity, intradermal irritation, sensitisation, genotoxicity, carcinogenicity . - <u>Chronic toxicity</u> is addressed in EN 30993-1 - <u>Immunotoxicity</u>: this hazard should be specifically addressed in the dossier taking account of the results of the risk analysis
Bleeding	<p>The effects of bleeding on the biological tissues as well as on the mechanical characteristics of the envelope are not known. For these reasons, it is suggested that, on the basis of the risk analysis, the manufacturer should provide the justification for the tests performed; he should also provide the results of the tests and the criteria used for accepting the estimated risk.</p> <p>The in-vitro test described in annex 1 of the present guidelines is provided as an example .</p>
Physical/ chemical incompatibilities	Data about compatibility between shell and filler must be available
Osmotic changes	Data about the osmotic situation must be available, if applicable
Interference with medical diagnosis and treatment	Information about possible interference with subsequent diagnosis and treatment must be addressed in the labelling
Lack of traceability	prEN 12180, 11.6 has to be applied
Limited lifetime	<p>Expected lifetime of implants (stability after implantation) must be addressed and documented using the information available (including results of animal studies). Data shall be available to justify expected lifetime of all components (durability and age related changes).</p> <p>The manufacturer has to provide adequate information in the instructions for use in relation to limitation of lifetime</p>
Unknown shelf-life	The use-by date based on stability data has to be given and is addressed in prEN 1041 and EN 980

2.2 Use of animal studies for estimating risks

As a general principle, in vivo animal studies may be considered as part of pre-clinical evaluation when the three following conditions are fulfilled:

- the risk analysis points out a lack of relevant data,
- no alternate appropriate ways for obtaining the missing data are available,
- such studies are likely to provide the missing data.

In particular, in vivo animal studies remain the only means to evaluate chronic toxicity and immuno-toxicity as well as ageing. They also constitute the only means to evaluate the biological effects of bleeding.

2.3 Clinical evaluation

The Notified Body shall, during the conformity assessment procedure, review the clinical evaluation in the technical file in compliance with MDD, Annex I, Section 1 in conjunction with annex X.

Clinical evidence covers all identified hazards, nevertheless, the main objective of the pre-market clinical evaluation is the estimation of the risks associated with the hazards due to local complications, including capsular contracture and rupture after implantation.

Clinical data to be provided by the manufacturer should originate :

- either from clinical investigations performed with the concerned prosthesis or with a sufficiently similar prosthesis, taking account of the objectives of the Study, and following a specific clinical investigation plan. Such clinical investigations should be performed when the risk analysis points out a lack of relevant clinical data.
- or from retrospective data obtained from previous use of the concerned prosthesis or of a sufficiently similar prosthesis, taking into account the objectives of the study

The acceptability criteria should be clearly documented and justified with a clear identification of the expected benefits to the patients.

2.4 Post-marketing surveillance

The manufacturer must institute and keep up to date a systematic active procedure defined in accordance with the results of the risk analysis, in order to gain and review experience from devices in the marketing phase including reviews of risk analysis and plans for any necessary corrective action. This systematic procedure should specifically include the review of data relating to long term effects, in particular those in relation to chronic toxicity.

During each surveillance audit the Notified Body shall review the experience gained by the manufacturer in the marketing phase and any subsequent action.

2.5 Hazards associated with the surgery and inherent hazards associated with the clinical use of breast implants

Information about the risks associated with surgery shall be provided in the labelling. These shall include:

1. clear indications for the use of the implant,
2. clear contraindications,
3. known adverse reactions,
4. a statement that breast implants are single use devices and must not be resterilized and/or reused.

Risks associated with lack of expertise of the surgeon and the need for follow-up of the patient shall be addressed.

There are certain risks particularly inherent in the use of breast implants or postulated from their use. These are addressed specifically during consultation between physician and patient and subject to informed consent.

A patient's card is an appropriate way to provide the involved parties with all the information needed during the life-cycle of the breast implants

Note: *The informative annexes IA, IB and IC attached to this document give examples of some particular pre-clinical tests, as well as an example of clinical investigation plan and of criteria of acceptability.*

The informative annex II provides an example of information to be provided to the patient prior to an implantation as well as an example of a patient questionnaire and of a patient consent form. These documents have been developed and issued by the European Committee on Quality Assurance and Medical Devices in Plastic Surgery (EQUAM).

3. REFERENCES

3.1 Standards

prEN 12180	Non active surgical implants – Body contouring implants – Specific requirements for mammary implants
prEN 14630	Non active surgical implants – General requirements
EN 550: 1994	Sterilization of medical devices – Validation and routine control of ethylene oxide sterilization
EN 552: 1994	Sterilization of medical devices - Validation and routine control of sterilization by irradiation
EN 554: 1994	Sterilization of medical devices – Validation and routine control of sterilization by moist heat
EN 556: 1994	Sterilization of medical devices – Requirements for devices to be labelled “Sterile”
EN 30993-1: 1993	Biological evaluation of medical devices - Part 1: Guidance on selection of tests
ISO/DIS 14538: 1996	Methods for the establishment of allowable limits for residues in medical devices using health based risk assessment
EN 1441: 1997	Medical devices - Risk analysis
EN 1041: 1998	Terminology, symbols and information provided with medical devices; information provided by the manufacturer with medical devices
EN 980: 1996	Graphical symbols for use in the labelling of medical devices (under review)

3.2 Reports

- * “Recommendations for evaluating breast implants prior to Marketing approval” (June 1997) :

Coordinators : Anne-Claude Koeger and Frédéric Fleurette.

Panel of experts : Daniel Marzin, Marc Pallardy, Gérard Ballon, Lise Barreau-Pouhaer, Nathalie Bricout, Monique Lê, Jean-Michel Nguyen, Claude Nicoletis, Jean-Marie Servant, Anne Tardivon, Henri Tristant.

Consulted specialists : Rosy Eloy, Marie-Françoise Harmand, Jean-Luc Jannic, Olivier Meyer.

- * “Silicone implants and connective tissue disease : evaluation of evidence for an association between the implantation of silicones and connective tissue disease”. Data published from end 1991 till July 1994. D.M. Gott and J.B. Tinkler. Published Medical Devices Agency, London 1994.

**ANNEX I A TO THE GUIDELINES FOR CONFORMITY ASSESSMENT OF
BREAST IMPLANTS (as mentioned in chapter 2)**

Informative annex relating to preclinical evaluation

This annex is mainly constituted by large extracts taken from the report of the experts group mentioned in chapter 3. It provides examples of some elements of preclinical studies which could be performed in the context of conformity assessment.

1. Abrasion resistance and analysis of abraded surfaces. The silicone elastomers of the shell are in fact relatively soft and susceptible to deterioration due to surface abrasion. When placed in the thoracic wall of a woman, they are subjected to permanent friction forces exerted by the soft parts above them.
2. Bleeding. An in vitro bleed test, identifying and characterising all the constituents remaining in the shell and all those that have passed into the solvent at the end of the test. In future, it would be desirable to carry out the test in two solvents, one consisting of an electrolyte solution and one containing lipoproteins. In fact, leakage is a secondary effect, currently unavoidable, for breast implants. The product of leakage may be dispersed in the body in two ways : simple diffusion in the extra-cellular liquid, or phagocytosis by peri-prosthetic macrophages. After a long period of leakage, which is theoretically infinite, and in the event of rupture of the implant, the product contained in the shell may present a different constitution from the initial filling material. It is necessary to know the composition of these products.

This in vitro bleed test is complemented by an in vivo bleed test. The contents of the explanted implant is analysed (composition of the silicones, cohesivity of the gel, etc.) a quantitative and qualitative analysis of the bleed products in the peri-prosthetic tissue and in the drainage ganglions is carried out.

3. Ageing. Comparison of the mechanical, physical and physical-chemical properties of implants (shell, filling material and complete implant) before and after ageing, in order to document any modifications of these same properties as a result of ageing is performed.¹

¹ The original report provides a list of tests to be performed. These tests are described in parts of that report which have not been reproduced in the present document. The tests performed for the comparison should be the same as those indicated in section 2.1 of the main part of the present document.

4. Evaluation of the biocompatibility of breast implants

4.1 Foreword

Generally, it should be noted, that there have been to date no tests carried out in bleeding conditions, i.e. involving the passage of the contents through the wall of the silicone shell.

All the following tests were carried out either on aqueous extracts or in a solvent, or by direct contact (cf. table in annex 1).

In order to establish bleeding conditions, it is important to define the extraction conditions, since it is on an extract that these tests are carried out, and the extraction conditions must reproduce the bleeding conditions.

The following points relate to the product of the extract :

- surface/volume ratio of at least 6 cm²/ml or 4 g/ml,
- extraction duration higher than that enabling the acquisition of a significant extract,
- extraction temperature :37°C,
- conditions of mechanical agitation whereby the implant is subjected to stress may permit the extraction duration to be reduced.

Finally it is vital that analysis of the composition of the extracts is carried out using sensitive and specific methods.

4.2 Evaluation of biological risks

4.2.1 *Evaluation of cytotoxicity* : in a standardised model, cytotoxicity is evaluated by direct or indirect contact (via the agar) lasting 24 to 72 hours with the material to be tested and/or on the extracts. The cells used are in general fibroblastic cell lines. The culture rarely lasts beyond 72 hours. The appreciation criteria relate to modifications to the metabolism, the cell cycle or the cellular viability.

4.2.2 *Systemic toxicity* : this systemic toxicity test may be carried out either intravenously or intraperitoneally. Bearing in mind the nature of the extracted molecules, it is preferable to carry out toxicity testing intraperitoneally in mice using 50 ml/kg of the extract or of a bleeding product injected peritoneally.

Survival and signs of toxicity are the analytical criteria.

It is also possible to endeavour to investigate activation signs, particularly of peritoneal macrophages (tissue plasminogen activators, or interleukins activation). This model should be validated for the silicones.

This model may be extended from 72 hours (time required for standards) to 15 days (by using repeated injections).

4.2.3 *Intradermal irritation test* : here again, this test investigates a local effect and the standard test may be applied. The question may simply be raised whether it is really relevant to carry out a test with one single intradermal injection of the product, bearing in mind the exposure conditions to products of bleeding in the human.

4.2.4 *Sensitisation tests* : these tests are treated in the immuno-toxicity studies

4.2.5 *Hemocompatibility tests* : these tests investigate the existence of an interaction between the products of bleeding and the blood cells or the major blood systems:

- coagulation activation,
- platelet system activation,
- fibrinolytic system activation or inhibition,
- complement system activation,
- haemolysis activation

These tests are in vitro tests carried out in static conditions using a control, in the presence of human blood, seeking for each of the systems explored the appearance or the appearance kinetics of a specific system marker :

- fibrinopeptide or coagulation time of the coagulation system,
- platelet activation markers: beta-thromboglobuline,
- complement activation: liberation of C3a, C5a or of the fraction of the terminal complex,
- hemolysis: measurement of the rate of haemoglobin after a contact period of 1 to 3 hours

4.3 Immunotoxicity tests

4.3.1 *Introduction* : certain pathological conditions associated with the implantation of breast implants are of immunological origin. By virtue of this fact, it is necessary to evaluate the impact of implantation of this type of material on the immune system. Immuno-toxicity studies will be included in the chronic toxicity testing and will be based essentially on a histology of the lymphoid organs. These tests should bring to light any effect of implants on the immune system and therefore indicate if it is necessary to proceed with supplementary testing. However these tests are not able to cast light on the potential of the material tested to induce auto-immune diseases. At the present time, there is no satisfactory approach concerning these aspects. The sensitisation potential will also be evaluated according to a conventional protocol using the recommendations of OECD guideline 406.

4.3.2 *Immunotoxicity study during toxicity tests by repeated administration*

4.3.2.1 Method and protocol : the end-product is tested along with the filler solution. The selected animal for the study is the miniature pig (only the female of the species is used). The practical details of the test protocol (doses, implantation sites, animal batches) are covered by the protocol for studies of chronic toxicity and by the OECD guideline 409.

At the end of the study and each time an animal is killed, samples will be taken of the following lymphoid organs : thymus, spleen, bone marrow, ganglions draining the implantation site, mesentery ganglions. For the thymus, a cortical/medullary zone ratio is calculated as well as the histopathological examination. For the ganglions, in addition to the histopathological examination, weight and cellularity data must also be supplied and the presence of germination centres is of particular interest.

For the implanted animals, a histological analysis is carried out on the fibrous shell surrounding the implant, involving investigation of the infiltrating granulocytes, monocytes and lymphocytes.

4.3.2.2 Analysis of results : in the event of histological alteration of the examined lymphoid tissues which shows a diminishing or modification of the cellular populations, it is necessary to proceed with further testing aimed at evaluating a possible immunosuppressive effect. The testing should take account of the latest scientific advances at the time the testing takes place. If there is an increase in the number of germination centres with relation to the controls in the ganglions or the spleen, it is necessary to proceed with supplementary testing designed to characterise this response. The testing should take account of the latest scientific advances at the time the testing takes place.

4.3.2.3. Sensitisation power study : this study is to be carried out according to the OECD 406 directives concerning the Magnusson and Kligman maximisation test. The materials tested will be the filling material and the shell intradermally. Several non-irritant concentrations will be tested in order to determine the minimal irritant concentration before this test is begun.

4.4 Genotoxicity study

4.4.1 *General* : the genotoxicity studies must enable evaluation of the genotoxicity of the filling material which may accidentally be released by rupture or by leakage within the organism and the genotoxicity of the end-product. In the event of the filling material representing too great a toxicity for one of the reactive systems (e.g. bacteriostatic activity in the case of bacterial tests), the test is replaced for this system by a test of the end-product and the filling material separately. The genotoxicity tests must be carried out before each clinical trial.

4.4.2 *Products* : where the products cannot themselves be studied, an extract of these products should be studied instead. Before any extraction or test, each material or device must be in its usage state, including all sterilisation processes (i.e. in the state in which it would be used clinically).

Two suitable extraction forms must be used, one with a physiological medium (e.g. 0.9% NaCl isotonic solute or cellular culture medium, the second with a solvent such as dimethylsulfoxide (DMSO) which is compatible with the testing system.

DMSO is known to be cytotoxic on mammal cells in the selected testing systems at concentrations higher than 5 g/l in an aqueous solvent. The greatest quantity possible per volume of extractant (expressed in cm³/ml or in g/ml) must be used.

The materials and devices hardened in situ must be tested in their state before and after hardening.

Extraction must be carried out in closed receptacles with a minimum overhead clearance.

4.4.3. *Test methods* : a sequence of at least 3 in vitro genotoxicity tests must be carried out on each extract. This sequence must comprise at least :

- one gene mutation on bacteria (in accordance with OECD guidelines 471-472),
- one on in vitro gene mutation test on mammal cells (in accordance with OECD guideline 476),
- one on in vitro chromosome mutation test on mammal cells (in accordance with OECD guideline 473),

In the event of conflicting test results or dubious results from one of the tests of this sequence, supplementary tests designed to show up any primary lesions of the DNA must be carried out in vitro (in accordance with the OECD guideline 482). In vivo tests for chromosome aberrations (in accordance with OECD guidelines 474 and/or 475) and for primary lesions of the DNA may be required.

4.5 Carcinogenicity study

4.5.1 *General* : the carcinogenicity study must enable evaluation of the local and systemic carcinogenic risk of the complete device but also of the filling material which may be released in the event of accidental rupture or as a result of leakage.

Carcinogenicity studies should be carried out before any clinical trial.

4.5.2 *Preparing samples*

Finished products : a properly shaped implant should be the basis of the test material when considering the carcinogenic potential of the solid state (Oppenheimer effect). The implant must be subjected to all the processes that an implant undergoes in clinical use.

Filling materials : the filling materials shall be injected subcutaneously into a site comparable to that used clinically once at the start of the test.

4.5.3 *Test methods* : carcinogenicity tests must be carried out using at least one species of rodent in accordance with OECD guidelines 451 or 453, after appropriate modification, for the materials to be tested in the conditions described above.

Implantation at the maximum implantable dose, which is the maximum quantity (dose) of an implantable material that a test animal may tolerate without harmful physical or mechanical effects, will be carried out once at the start of the study. The animals from the negative control batch will undergo the same operative treatment as the implanted animals (i.e. anaesthesia, implantation operation, etc..). At least 4 batches of animals will be used :

- batch 1 : negative control receiving the 0.9% NaCl isotonic solute subcutaneously,
- batch 2 : receiving the filling material subcutaneously,
- batch 3 : implant containing 0.9% subcutaneously,
- batch 4 : implant containing material meant for human implantation

In the case of a filling material, the carcinogenic potential of which has already been evaluated subcutaneously in one species of rodent, in the conditions described above, this type of study may be limited to the implementation of batches 1 and 4.

In addition to the tissues examined macroscopically and histologically, the surrounding tissues and the ganglions draining the implantation point should also be included.

4.6. Chronic toxicity studies

4.6.1 *General*

The chronic toxicity studies must enable evaluation of the potential local and systemic toxic effects of the complete device but also of the filling material which may be released in the event of accidental rupture or as a result of leakage.

Chronic toxicity studies should be carried out before any clinical trial. Testing should be carried out on at least one non-rodent animal species, where implantation of the product designed to be used on women is possible.

This study is accompanied by the biodistribution study (paragraph 4 of this chapter) and the immunotoxicity study (chapter on ‘Immunotoxicity Studies’).

4.6.2 *Products administered*

Solid products : where possible, the device must be tested in its condition for use. If this is not the case, an appropriately shaped implant must be composed from the test material.

Filling materials : the filling materials are to be injected subcutaneously in a site comparable to that used clinically once at the start of the test.

4.6.3 *Tests methods*

The chronic toxicity tests must be carried out in accordance with OECD guidelines 408 and 409 after appropriate modifications to the materials to be tested in the conditions described above.

The studies are limited to female animals.

The duration of the studies must be at least 1 year after administered implantation. Implantation at the maximum implantable dose (which is the maximum quantity {dose} of an implantable material that a test animal may tolerate without harmful physical or mechanical effects : this maximum implantable dose must, for larger animals, include several implantation sites) will be carried out once at the start of the study. All the animals will undergo the same operative treatment (i.e. anaesthesia, implantation operation, ...)

At least 4 batches of animal will be used :

- batch 1 : negative control receiving the 0.9% NaCl isotonic solute subcutaneously,
- batch 2 : receiving the filling material subcutaneously,
- batch 3 : implant containing 0.9% NaCl,
- batch 4 : implant containing material meant for human implantation

In the case of an implant containing only the 0.9% NaCl isotonic solute, only batches 1 and 3 are relevant.

In addition to the tissues examined macroscopically and histologically, the surrounding tissues (involving investigation for infiltrating monocytes and lymphocytes) and the ganglions draining the implantation point should also be included. Part of the peri-prosthetic tissues and the ganglions will be used for a qualitative and quantitative evaluation of the migration of the filling material.

In the case of a filling material, the toxicity of which has already been evaluated subcutaneously for at least one year in a non-rodent species, in the conditions described above, this type of study may be limited to the implementation of batches 1 and 4.

For a species in which it is possible to implant the product in the form designed for human implantation, one animal per batch will be killed at 3 to 6 months in order to study local tolerance (examination of the peri-prosthetic and ganglion tissue and evaluation of the migration of the filling material, along with physical-chemical and mechanical study of the explanted implants).

- 4.6.4 *Kinetics of toxicity* : the objective of this model is, during chronic administration, to identify the organs targeted by the bleeding. Dosages are carried out on animals that have received implants and been injected with the filling material. The detection of the distribution of these products is then carried out in the blood, liver, spleen, brain, kidney and lung, using appropriate methods. The examination sequences are carried out as soon as the animals are killed.

**ANNEX I B TO THE GUIDELINES FOR CONFORMITY ASSESSMENT OF
BREAST IMPLANTS (as mentioned in chapter 2)**

Informative annex relating to clinical evaluation

This annex is mainly constituted by large extracts taken from the report of the experts group mentioned in chapter 3. It provides an example for a method of clinical evaluation using data obtained from a prospective clinical trial.

I. OBJECTIVES

The purpose of the pre-market clinical evaluation is to estimate the frequency at which complications occur as a result of the implantation of breast implant. Two types of complication may occur : local and general.

General complications occur infrequently, if at all. They cannot therefore be evaluated within the framework of a prospective clinical trial carried out prior to marketing approval. A large number of patients would have to be recruited, monitored over several years and compared with a reference group. But, any occurrence of this type of complication will have to be declared, then analysed within the framework of the post-marketing surveillance. This applies both for connective tissue diseases and other, as yet unidentified, diseases.

Local complications occur on a much more frequent basis than general complications, but, paradoxically, have been less evaluated than the latter. Local complications can be either peri-prosthetic contractures of the implants or ruptures and sudden or progressive collapse. Peri-prosthetic contractures would be the first and most frequent local complications. These may lead to pain, aesthetic damages and, eventually, further surgical intervention. Ruptures would occur less frequently than the contractures, but would almost always require further surgical intervention. This also applies in the case of collapse.

The risk of these complications occurring needs to be analysed, since this can potentially negate the benefits for women receiving breast implants. This risk, as opposed to the risk of general complications, can be analysed in the framework of trials carried out prior to authorising the marketing of breast implants. Post-marketing surveillance must also be carried out so that the long term evolution can be specified.

In addition to evaluating these risks, which is essential, other complications could be studied, for example, local-regional post-operative rate of infection, hematoma, badly positioned implant, folding, pain and local-regional inflammation during the monitoring period. These complications are, however, more related to surgical conditions and to the

medical context, than to the actual material, except perhaps for inflammatory phenomena and pain.

II. BREAST IMPLANTS CONCERNED

All types of internal breast implants, containing isotonic solution, silicone gel or other types of filling material, are exposed to the risk of local complications.

As a consequence, manufacturers need to analyse these risks for each type of implant they wish to produce commercially.

If modifications are made by the manufacturer following authorisation for marketing, those concerning the nature of the shell, the filling material and any device incorporated in the implant may require further evaluation.

With respect to the shell and any device incorporated in the implant, any major modification must be followed by both toxicological evaluation and a new evaluation of the risk of local complications.

If a new filling material is used, it is essential that a toxicological evaluation of the new material and its interaction with the shell is carried out. However, an evaluation of local complications must also be made.

III. METHODS OF OBTAINING CLINICAL DATA

An appropriate method of evaluating the risk of local complications caused by breast implants is that of a prospective clinical trial carried out prior to their authorisation for marketing. The recommendations for carrying out such trials are presented in this document.

The European Directive presents the information extracted from the literature as a possible alternative to carrying out prospective clinical trials. However, the information published does not always enable the data and results to be controlled in the case of an implant which a manufacturer wishes to commercialise. Thus, a clinical dossier must be put together on the basis of trials that have already been performed. This dossier should therefore be subject to retrospective analysis using the evaluation criteria described in this document. Therefore, with respect to the methodology, this retrospective approach is the only acceptable alternative to the prospective clinical trial.

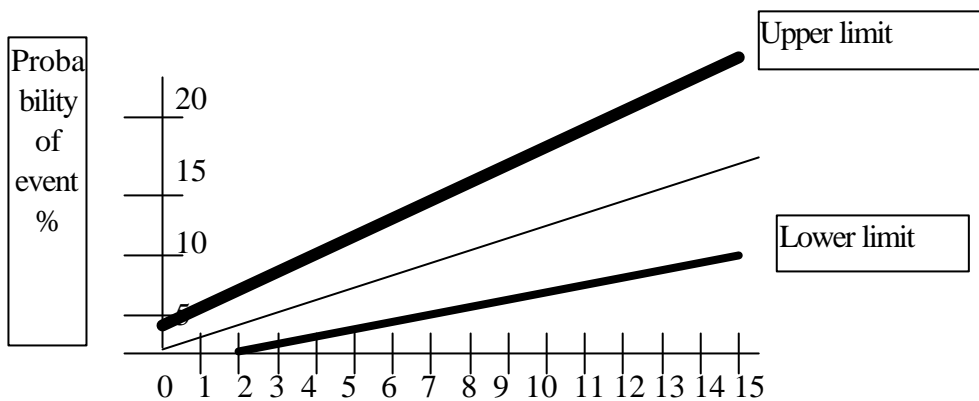
IV. METHODS OF CARRYING OUT THE PROSPECTIVE CLINICAL TRIAL

Only breast implants having satisfied the pre-clinical evaluation presented in the part one of this document could be used for clinical evaluation in patients.

1. Methodology

- * The group of patients should consist, on the one hand of those whose surgical indication was reconstruction following breast cancer, and on the other hand of those surgical indication was implantation for aesthetic purposes. A one third (reconstruction) – two thirds (aesthetics) distribution is desirable, except for implants which are to be used exclusively for one of these operative indications.
- * The minimum duration of the following-up will be 2 years for each patient.
- * The total number of implants evaluated should not be less than 150. If two prostheses are implanted in the same patient, these could be evaluated independently. Providing that all the patients have been monitored for at least 2 years, a total of 150 implants will enable the following to be estimated :
 - = a rate of rupture of 1% with a 95 % confidence interval of between 0 and 4%,
 - = a rate of peri-prosthetic contracture of 5% with a 95% confidence interval of between 2% and 10% (see graph below)

5% confidence intervals for a sample of 150 prostheses



Number of ruptures or contractures at 2 years

In order to reduce the variation in estimating the rate of peri-prosthetic contracture, it is preferable, where possible, not to include patients who have had the following :

- a previous breast implant,
- a recurrence of breast cancer,
- a previous breast radiation treatment.

In order to reduce the number of “missing” patients, it is recommended not to include the following :

- patients residing in a foreign country,
- patients who reside too far away from their monitoring centre.

* Choice of diagnostic methods :

The diagnosis of local complications is first made or suspected through the clinical examination. If rupture of the prosthetic integrity is diagnosed, this should be completed using an imaging technique. A single digital mammogram (external costal profile) is sufficient. If any doubt remains, a second mammogram with compression of the breast (external oblique) may prove necessary. An additional mammary ultrasound examination is required only in the case where, in spite of two mammograms, doubt still remains.

* Choice of investigating surgeon(s) and radiologist(s)

The choice should be made by the promoter of the clinical trial. The promoter will be responsible for ensuring that the investigators respect the legislation in force, including the legislation transposing annex X of MD directive and annex 7 of AIMD directive (see also EN 540)

= The surgeon(s) should have the necessary qualifications and sufficient implantation experience (50 implants per year). They should perform the operations themselves on the patients included in the clinical trial (i.e. without delegating the task)

= The radiologist(s) should be experienced in the imaging of women with breast implants. They should perform the radiographic examination specified in the protocol themselves (i.e. without delegating the task).

<p style="text-align: center;"><u>ANNEX I C TO THE GUIDELINES FOR CONFORMITY ASSESSMENT OF BREAST IMPLANTS</u></p>

Informative annex relating to evaluation and acceptability criteria to be
used for the clinical evaluation.

This annex is mainly constituted by large extracts taken from the report of the experts group mentioned in chapter 3. It provides an example for evaluation criteria, evaluation procedure and acceptability criteria.

I. EVALUATION CRITERIA

Accurate details cannot always be given on the evaluation criteria, since they depend on current knowledge of the subject.

* Evaluation of the peri-prosthetic contracture

The Baker classification will be used as a reference for this evaluation. This classification defines four stages :

- = stage I : completely nature appearance of the breast, as if there was no implant
- = stage II : minor peri-prosthetic contracture ascertained by simple palpation of the breast. The patient feels no discomfort
- = stage III : moderate peri-prosthetic contracture ascertained by clearer perception of the implant on palpation. The patient also perceives some hardness
- = stage IV : severe peri-prosthetic contracture ascertained visually. Increased symptoms.

Only stages III and IV will be classed as peri-prosthetic contractures.

* Evaluation of ruptures and of sudden or progressive collapse

- There are certain clinical signs which may lead to suspicion of prosthetic rupture, possibly requiring radiological exploration :
 - = collapse of the breast if the implant contains a re-absorbable or biodegradable filling material,
 - = change in the volume, shape, consistency of the breast and its cutaneous appearance,
 - = peri-prosthetic contracture occurring after an interval of one year,
 - = appearance of local-regional inflammatory signs.

This list is non-exhaustive. Ruptures of silicone implants may arise occasionally without any clinical signs.

- During the mammographic examination, the diagnostic signs are as follows :

= for breast implants filled with silicone gel :

- a) Near certainty of normality : visibility of superficial folds in the shell
- b) Doubts on the normality : poor visibility of superficial folds in the shell
- c) Near certainty of rupture confirmed by at least one of the following signs: visible enlargement of the implant, spontaneous visibility of the shell collapsed into the gel, direct visibility of the breach, direct visibility of the extra-capsular intrusion of the silicone gel, and less specifically : presence of watery liquids mixed with the silicone.

= for other types of implants, the rupture may be confirmed by direct visibility of the collapse :

The visibility of an intra-capsular liquid effusion is an indirect sign as it is less specific than a rupture diagnosis.

During the ultrasound examination, the rupture of a breast implant filled with silicone gel may be suspected if one of the following signs is apparent :

- * heterogeneous echostructure of the silicone gel,
- * presence of hyper-echogenic double lines (rails) in the gel,
- * snowstorm appearance (extra-capsular leakage). The ultrasound examination also reveals certain intra-capsular effusion.

The protocol should specify action to be taken when faced with :

- * near certainty of clinical rupture (radiographic investigation or removal of the implant),
- * near certainty of clinical and radiographic rupture (systematic removal or not),
- * any doubts on the integrity of the prosthetic cavity in spite of the radiographic investigation (whether or not ablation of the implant is required).

II. FREQUENCY AND NATURE OF THE FOLLOW-UP

- * Clinical follow-up

Clinical monitoring will be guaranteed at least four points in time following implantation of the internal mammary prosthesis : at 1 month, 6 months, 1 year and 2 years.

During each of these examinations, the clinical information specified in the "Evaluation criteria" paragraph should be collected.

Outside of this framework, any patient should be examined by his surgeon if new clinical signs appear. Equally, any associated pathologies should be noted. This information will also be reported in the observation record file.

* No biological evaluation is required

It should be noted that toxicological and immunological evaluation will have been carried out previously. However, biological examinations could be performed at the surgeon's request. Obviously, these tests should be carried out as soon as clinical signs of a general illness become apparent, in particular those for a connective tissue disease.

* Radiological follow-up

- If there is no incident which causes prosthetic deflating or rupture to be suspected during clinical follow-up or during spontaneous visits, a single evaluation will be performed at the end of the clinical trial, i.e. at 2 years for each patient and each implant. This evaluation could be performed at an earlier date if the patient is due to move away from the area.
- If a rupture is suspected during clinical follow-up (compulsory or spontaneous visit), a radiological evaluation will be performed. The results must be recorded in the observation record file.

III. COLLECTION METHODS FOR THE CLINICAL AND PARACLINICAL DATA

This data are recorded in accordance with a reference model (see EN540)

Clinical information must obligatorily be collected by the investigative surgeon who operated on the patient.

Radiographic information must obligatorily be collected by the radiologist who carried out the examination.

This information should be sent to the person in charge of the clinical trial.

Besides the clinical and radiological data concerning the evaluation criteria, other information must be collected. This involves in particular :

- * the precise description of the implant and the identification number,
- * the date of implantation,
- * the surgical indication (reconstruction or cosmetic),
- * the operative technique used,

- * certain information about the patient :
 - = date of birth,
 - = medical/surgical history (in particular, cardio-vascular illnesses, hemostatis diseases, diabetes, connective tissues),
 - = smoker/non-smoker,
 - = weight/height

In the event of ablation of the implant, whatever the cause, the collected information must contain at least :

- * the clinical and radiological factors and any other examination having led to the ablation of the implant,
- * in the event of a reported rupture, the (probable) date and the circumstances of the incident,
- * in the event of general complications, the examinations which enabled the diagnosis(es) and the date that the first symptoms appeared.

Finally, the product of the ablation, comprising the implant and one or two peri-prosthetic tissue fragments, must be analysed as follows.

In the event of bilateral explantation for unilateral rupture, the damaged and undamaged implants are submitted to the following trials.

The mechanical and physical-chemical properties of the undamaged implants should be documented.

For the damaged implants, and in the absence of a large rupture, only the physical-chemical properties of the gel inside the implant are analysed :

- . histological study of the peri-prosthetic tissue of damaged and undamaged implants,
- . identification of the cellular sub-populations of the infiltrates.
- . investigation in particular of granulomas.

For undamaged implants, quantitative and qualitative analysis of the silicones present in the peri-prosthetic tissue.

If the excision of satellite ganglions is considered necessary, the ganglion samples are to be studied, whether or not the implant is damaged, in addition to the standard histology, weight, cellularity, particular existence of germination centres, and quantitative and qualitative analysis of the silicones.

IV. ANALYSIS AND PRESENTATION OF THE RESULTS

It must include :

- * an analysis per patient and per implant,
- * a global analysis of the population per item,
- * an analysis in sub-group in terms of the indications (for reconstruction or for aesthetic purposes),
- * an analysis of the clinical evaluation criteria by the Kaplan-Meier method, carried out globally and for each instruction group,
- * a presentation of the complication rates with their 95% confidence interval according to the exact binomial method,
- * missing data concerning the Baker classification or radiographic evaluation, lost files or interrupted follow-up of a patient should lead to additional specific investigations. In the absence of such investigations, these elements may be considered as the worst result, i.e. : a Baker stage IV or a rupture.

V. LOGISTICS

- The data must be recorded in observation record files(see EN 540);
- In order to ensure an adequate match between the number of inclusions and the number of actual implants (to avoid non-declaration in the case of a bad operative result or monitoring), a counterfoil record will be required for delivery of the implants;
- The implants delivered by the promoter must include a unique identification number (engraved on the implant) which will be the same as that on the counterfoil record. A (carbon) copy of this record must be sent to the body responsible for judging the dossiers;
- The protocol must furthermore provide for quality assurance of the clinical trial and of the procedures to be implemented in the event of a control of this trial.

VI. RETROSPECTIVE ANALYSIS METHOD FOR EXISTING DATA

The validation of this evaluation may be carried out on existing data, if the whole of this pre-existing data can be found by the promoter, i.e. :

- A study involving at least 150 implants taken from one or several series. Each of these series must be consecutive;
- Results concerning mammography evaluation after two years for each implant, or even longer;
- Results concerning the clinical evaluation of :

- * peri-prosthetic contracture (Baker classification) at regular intervals at least up to two years after implantation of the breast implant,
- * prosthetic rupture at regular intervals for up to at least two years; the same applying to collapse.

Furthermore analysis and presentation of data and results must conform with the criteria defined in section IV of the present Annex.

VII STATISTICAL CRITERIA FOR JUDGING THE MAGNITUDE OF THE IDENTIFIED RISK

One of the arguments in the decision to authorise or refuse marketing of an implant is the value of the upper limit of the 95% confidence interval for the rates assessed in clinical trial. This value in fact corresponds to the value which could be observed potentially in the population if the breast implants were marketed.

The table below presents the upper limits of the unilateral 95% confidence interval (according to the exact binomial method) in terms of the number of observed events and the size of the clinical trial sample. These limits feature in italics in the table.

		Number of implants studied			
		100	150	500	2000
Number of events : rupture or contracture	0	<i>2,95</i>	<i>1,97</i>	<i>0,59</i>	<i>0,29</i>
	1	<i>4,65</i>	<i>3,12</i>	<i>0,94</i>	<i>0,47</i>
	2	<i>6,16</i>	<i>4,13</i>	<i>1,25</i>	<i>0,62</i>
	3	<i>7,57</i>	<i>5,08</i>	<i>1,54</i>	<i>0,77</i>
	4	<i>8,91</i>	<i>5,99</i>	<i>1,82</i>	<i>0,91</i>
	5	<i>10,22</i>	<i>6,88</i>	<i>2,09</i>	<i>1,04</i>
	6	<i>11,49</i>	<i>7,74</i>	<i>2,37</i>	<i>1,18</i>
	7	<i>12,74</i>	<i>8,58</i>	<i>2,61</i>	<i>1,31</i>
	8	<i>13,97</i>	<i>9,41</i>	<i>2,86</i>	<i>1,43</i>
	9	<i>15,17</i>	<i>10,23</i>	<i>3,12</i>	<i>1,56</i>
	10	<i>16,37</i>	<i>11,04</i>	<i>3,36</i>	<i>1,69</i>

Thus, for a trial involving 100 breast implants, even where no rupture has been identified after two years of monitoring, it is possible for a rupture rate of 3% to be observed if this implant is more widely distributed.

By the same token, for a trial involving 150 implants, if two ruptures have been identified after two years of monitoring, it is possible for a rupture rate of 4% to be observed if this implant is more widely distributed.

The same applies to peri-prosthetic contractures.

Surgeons consider that the maximum acceptable rate for ruptures after two years is 4%. Consequently, a trial involving 150 implants should not give rise to more than one rupture.

For the peri-prosthetic contractures, after aesthetic surgery, the experts consider that the maximum acceptable rate after two years is 9%. Consequently, a trial involving 150 implants should not give rise to more than seven peri-prosthetic contractures. This acceptability rate could be reconsidered for reconstructive surgery after breast cancer.

This is to inform you about the options you have as well as about the risks and possible side effects. This brochure is designed to give you all the information you need to make your decision. Please read this form carefully before discussing the details with your physician.

The following statements are based on current scientific knowledge, but there is still research going on in this field.

There is always a reactive response to every foreign material implanted in a human body, which should not be confused with auto-immune disease.

Multiple large scientific studies have not demonstrated a link between auto-immune diseases and implantations of silicone implants.

Existing disease predisposition may be further strengthened in case of unspecific activation of the immune system due to any implant.

Recent studies indicate clearly that silicone breast implants do not increase the incidence of breast tumors in women.

Polyesterurethane coated breast implants pose an unquantifiable but extremely low carcinogenic risk. However, the U.S. health authorities estimate this risk to be below 1 : 1 million.

Published data on damage to breast fed children of mothers with silicone gel filled implants are lacking valid scientific evidence.

Which risks and side effects could be related to breast implants ?

The human body will always produce a fibrous capsule to surround a breast implant.

This capsule may shrink and/or calcify. Subsequently the breast can be painful and firm. The aesthetic result may be unfavourable.

The risk to developing this complication is higher if you have had radiotherapy. The implant may move and/or change shape as a result of contracture. Then a surgical correction might be necessary. Please be aware of the fact that capsular contracture can also occur after a previous correction.

To break the capsule by application of pressure only (so called 'closed capsulotomy') should not be performed anymore, because of increased risk of rupture.

If the implant is positioned under the breast muscle, the position of the implant may be distorted when you move your arm.

Sometimes rippling of the skin over the implant surface is visible, when the implant is located underneath the skin (particularly in very slender individuals).

The life span of an implant is limited; therefore there may be a need for a replacement or removal. The manufacturers of your implant will provide data about rupture rates.

Therefore you should have your implant examined regularly. In general the following time intervals are considered to be appropriate : one month after surgery, six months after surgery, twelve months after surgery and after then every twelve months.

Pain, decreased breast size, nodules or uneven appearance of the breast could occur along with implant failure. If any of these symptoms occur, you should contact your physician immediately.

If the implant is suspected to have a defect it needs to be removed and, if you wish, to be replaced.

Gel bleeding means that gel passes through the shell of an implant. This occurs in every gel filled implant. The amount of gel bleeding depends on the design of the device. Normally the gel that passes through the shell remains within the capsule, but absorption of silicone into other tissues or organs can occur.

Silicone in these tissues can also originate from other sources, since silicone is used widely in medicine and in many products used in daily life.

Mammographies in patients with silicone gel filled implants are more difficult to interpret. Therefore you must inform your radiographer that you have silicone implants before mammography. Computerized mammography by an experienced radiographer may be a method for confirming a rupture. An echography of the breast is only indicated as a complement when a doubt remains. If mammograms do not give enough information magnetic resonance imaging (MRI) is strongly recommended.

MRI is also indicated if rupture, deflation or leakage suspected.

The most frequent malignant tumour in women is breast cancer. There is no increased occurrence of breast cancer in patients with breast implants. Nevertheless detection of a tumour by palpation or by mammography can be more difficult when implant surgery was performed. Your physician will discuss your individual risk for breast cancer disease with you.

Which risks and side effects could be related to every operative procedure?

Major bleeding during or after the procedure may require another operation and/or blood transfusion.

Local infection is rare but can occur. It could be a possible source of wound healing problems. In stubborn cases the removal of the implant might be necessary.

The risk of developing thrombosis (blood clots) after surgical procedures cannot be eliminated completely. This is one of the reasons why a hospital stay is highly recommended.

Preventive measures to minimise these risks will be discussed with you. Preparation for surgery and pre-operative measures also carry some risks. For example it is possible that nerves or vessels may be damaged by injection or infusion catheters (inflammation of veins, thrombosis).

There is also a small risk of infection with these measures (for example injection abscess).

It is extremely rare that blood transfusion or transfer of blood components become inevitable. In these cases a risk of infection with viral diseases (e.g. hepatitis, HIV) cannot be ruled out completely.

However the rate of infection is extremely low.

What happens after the operation ?

Please take note of the following facts :

Discoloration of the skin, loss of sensitivity and some feeling of tenseness are normal for the early postoperative period. These symptoms generally disappear within a few weeks.

Sensitivity of the nipple might be reduced temporarily or permanently.

The ability for breast feeding is maintained in most of the techniques (applies only to augmentation). Nevertheless we suggest that in case of pregnancy you should see your physician for a check-up and discuss your ability to breast feeding with him/her.

Please avoid activities in which you need to work with the muscles of your arm (carrying heavy things, tennis, etc.) for at least six weeks.

Please postpone taking showers, a bath or swimming until your physician allows you to do so.

After having received an implant, your doctor will inform you whether massaging of the implant is indicated. He/she will also tell you how long you need a special bra or a breast compression garment.

What can be achieved by a breast reconstruction procedure ?

We aim for the reconstruction of your breast, so that the shape has an aesthetic and natural appearance. This can be achieved by an implant or by your own tissues. In some patients reconstruction can be done immediately after the mastectomy procedure within one anaesthetic procedure. If this is not possible, breast reconstruction can always be performed later on.

If additional therapies (like chemotherapy or radiation) are necessary, we will recommend a delay of the reconstructive procedure until these therapies are completed.

Simultaneously or later on the size and shape of the opposite breast can be adjusted to the reconstructed one. In most cases an aesthetically satisfactory result can be achieved.

Nevertheless no surgeon can guarantee, that the result will be completely symmetrical.

Please consider that nowhere in nature is complete symmetry found.

The ability for breast feeding and full sensitivity of the nipple can not be restored.

(schema to be inserted)

What can be achieved by an augmentation procedure ?

We aim for the augmentation of your breast so that the shape and size have an aesthetic and natural appearance.

Particularly in patients with different breast sizes it can be difficult to achieve symmetry.

Please consider that nowhere in nature is complete symmetry found.

In order to enlarge the breast, usually a silicone device is implanted. In case that the enlargement should be achieved by using your own tissue, we give you special information about this procedure.

A small incision along the underside of your breast or along the areola of your nipple or in the axilla will be used. A pocket for the implant will be formed above or behind the breast muscle.

If a small and loose breast is enlarged, it might be necessary to perform a mastopexy with removal of excess skin and repositioning of the nipples to the original level. This procedure creates additional scars.

Full sensitivity of the nipple and the ability for breast feeding might be reduced after an augmentation.

(schema to be inserted).....

The selection of procedures

Usually general anaesthesia is used for all the above mentioned procedures. In selected cases local anaesthesia can be sufficient.

There are different types of implants which consist totally or partly of silicone. Your physician will explain the advantages and disadvantages of the different types and he/she will suggest the appropriate type of implant for you.

The procedures we suggest for you are marked :

Implantation of breast implant

- a) with silicone
- b) with textured surface silicone
- c) polyesterurethane foam coated surface
- d) by implantation of a silicone device, called a tissue expander, which will gradually be filled postoperatively with increasing amounts of saline solution until there is enough expansion of the skin. The filling phase normally takes between four and ten weeks. Two to five

months later the expander can be removed and a permanent implant will be inserted. There are also expander implants available which do not need to be exchanged.

- Filled with :
- a) silicone gel
 - b) saline
 - c) silicone gel and saline
 - d) other filler substances (.....)
- Implanted :
- a) under the pectoral muscle
 - b) above the pectoral muscle

Breast implants patient questionnaire

Dear patient,

The more we know about your history the better we can judge your risks. Please answer the following questions. We would be happy to assist you in doing so.

1. Do you take medication ?

Pain medication (for example Aspirin) or any other medication that interferes with the blood clotting system (for example Marcurriar, Heparin), sleeping pills, laxatives or contraceptives and/or other medications

Type / dose/.....

2. Do you smoke ?

If yes : how many cigarettes per day ? •
No

3. Are you allergic or sensitive to food, medication, tapes, rubber or ...?

• Yes, type •
No

4. Did you ever develop red, raised or wide scars?

• Yes •
No

5. **Do you have a tendency (you or relatives related by blood) to develop frequent nasal bleeding or prolonged bleeding after injuries or for developing blue spots without injury ?**

- *Yes, type* •
- No*

6. **Do you or relatives related by blood suffer from haematological (blood related) diseases and/or autoimmune disease (for example Lupus erythematoses, sclerodermia, rheumatic arthritis, vasculitis) ?**

- *Yes, type* •
- No*

7. **Do you frequently suffer from swelling or pains in your joints ?**

- *Yes, type, location*..... •
- No*

8. **When you are exposed to cold : do you suffer from severe pains of your hands and/or do your hands turn white in the cold ?**

- *Yes* •
- No*

9. **Do you suffer from stiffness of your hands, feet or knees in the morning ?**

- *Yes* •
- No*

10. **Do you experience a strong feeling of tension of your skin, of your face, your arms or your legs frequently?**

- *Yes* •
- No*

11. **Is it possible that you are pregnant?**

- *Yes* •
- No*

12. **Did you or do you suffer from any other disease (for example neurological or psychiatric disorders, diabetes, imbalance of hormones, etc.)?**

- *Yes, type*
- No*

Breast implants patient declaration of consent

I have read the informative part of this form. I will follow the instructions carefully.

I have answered all questions to my best knowledge.

During the interview with Dr we discussed the following :

Selection of procedure, advantages and disadvantages of the different techniques, individual circumstances which might increase the risks, possible complications, additional surgical procedures, probability of blood transfusion, possibility of the use of my own blood as well as :

.....
.....

I have been allowed to ask all questions which concern me as follows :

.....
.....

My questions were answered completely and in an understandable way.

Declaration of consent

After careful consideration I authorize Dr to perform the following procedure :

.....
.....

I accept the need for changes or additional surgical procedures of the selected technique, if necessary.

Yes

No

I am aware of the fact that I have to go for regular check-ups.

In case I develop pain or any other signs which indicate that there might be a complication I shall contact my physician immediately.

Date :

Signature :(patient)

Signature :(witness)