B. Design and construction

B.I. Product description :

P.I.P.'s breast implants are sterile and high cohesivity silicone gel pre-filled. Each implant is protected by a double packaging, which guarantees the implant sterility and a better asepsia during the manipulation conditions.

P.I.P. pre-filled breast implants are made on the following way :

- A container : sterile and biocompatible envelope manufactured from silicone elastomers of medical grade,
- A containing product : sterile and biocompatible high cohesivity silicone gel

B.II. Indications for use :

Breast implants in general are used in plastic surgery for :

- breast augmentation : consisting of increasing the breast volume by implant insertion,
- breast reconstruction : further to total or partial removal of the injured or cancerous (mastectomy) mammary gland.

P.I.P. breast implant must not be used :

- in the case of infection,
- in the case of systemic disorders,
- on a patient with unsuitable or damaged tissue cover,
- on a patient having previously had a problem with breast implants,
- in the case of psychological frailty of the patient.

B.III. Proposed variants :

High cohesivity gel pre-filled breast implants are made up of several variants :

- profile,
- surface type,
- volume.

B.III.1. Profile :

P.I.P.'s pre-filled breast implants can have a different shape / profile.
Five different profile types can be found :

- standard profile (S),
- high profile (H),
- extra high profile (EH)
- reconstruction profile (R),
- asymmetrical profile (AR or AL).

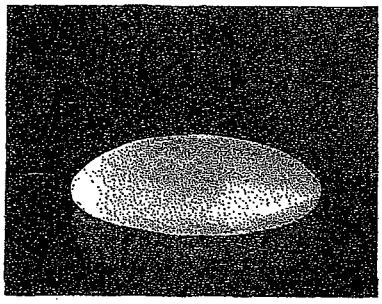
The first three profiles (standard high and extra high) are hemispheral profiles. For a given volume, the main characteristics of the implant are the projection / height and diameter.

To an equivalent volume, a standard profile projection is lower than that of a high profile whereas its diameter is greater.

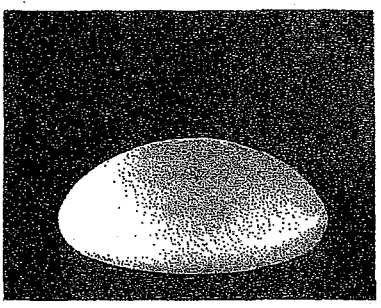
The extra high profile was studied under the basis of the "over-filled" high profile so as to increase the implant projection.

Reconstruction profiles have a slightly more complex shape, in so far as the implant shape is closer to that of a breast. That's the reason why the reconstruction profile designation was linked to this type of implant. In case of reconstruction surgery consecutive to the breast removal, this implant type helps filling in the total or almost total absence of mammary gland.

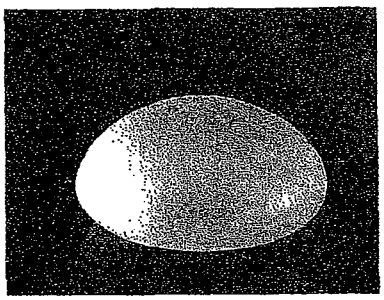
The asymmetrical profiles have no symmetry axis and can be divided into two categories : left side (AL) and right side (AR). This implant shape was studied so as to fit the patient gland, the pectoral muscle, the surrounding fibrous tissues.



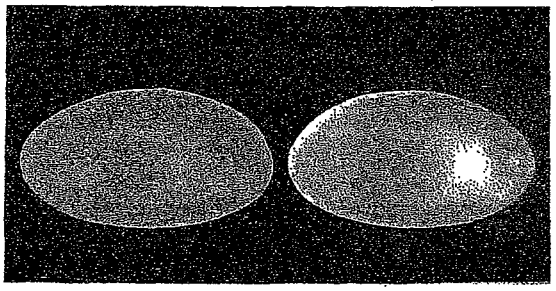
Profile S



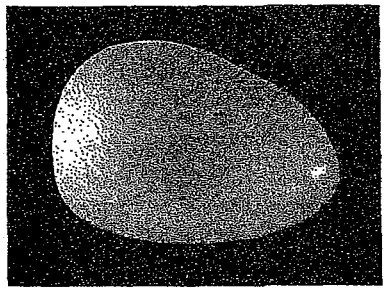
Profile H



Profile EH



Profiles AR and AL

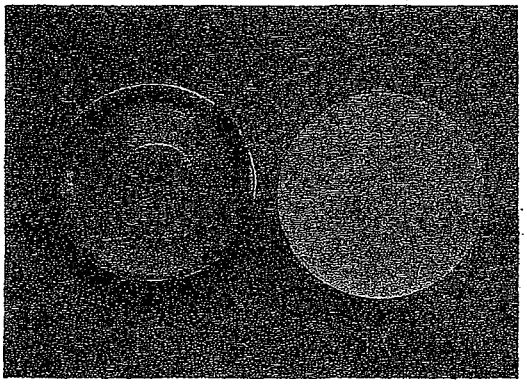


Profile R

B.III.2. Surface :

The external structure of the high cohesivity gel pre-filled breast implant envelope can be of two types :

- smooth surface (LS),
- textured surface (TX).



For asymmetrical and reconstruction profile breast implants :

Given the non symmetrical shapes of these profiles and taking into account the distortion applied to the prosthesis when introducing it into the body, a location system (tactile and visual) allows guiding the surgeon when implanting the device so that it is positioned on the right side inside the patient body.

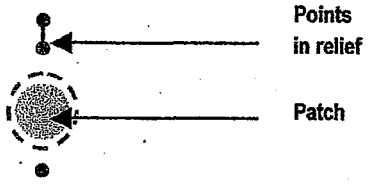
Smooth surface breast implants can slide, which is not disturbing for a hemispheral profile (symmetrical), but becomes so for asymmetrical and reconstruction profiles.

Asymmetrical and reconstruction profile implants always have a textured surface.

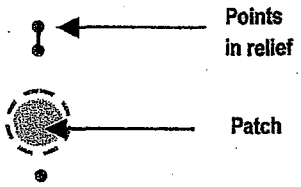
➢ ***Tactile location system :***

For the submammary and axillary implantation incisions, the asymmetrical and reconstruction prosthesis has a tactile location system allowing to distinguish the top from the bottom.

These are points in relief in silicone elastomer at the back of the implant, on the patch side.
The top of the implant has two points in relief and the bottom one point.



Asymmetrical profile back drawing



Reconstruction profile back drawing

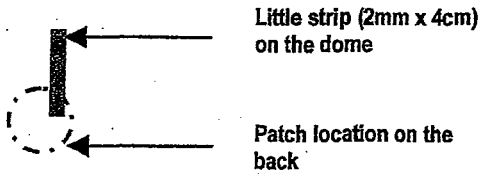
➢ ***Visual location system :***

For the peri-aerolar implantation incision, the prosthesis has a visual location system on the implant dome (side opposed to the patch) allowing to position the implant in the right axis and also to locate the implant top or bottom.
This visual location system consists in the absence of texturing elements of rectangular shape, measuring out 2 mm x 4cm.

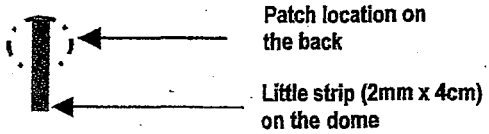
This little strip is positioned on the implant dome :

- on the asymmetrical profiles: on the implant superior half
- on reconstruction profiles: on the implant inferior third

It represents the prosthesis vertical axis



Asymmetrical profile drawing



Reconstruction profile drawing

B.III.3. Volume :

The range of P.I.P.'s high cohesivity gel pre-filled breast implants gathers several volumes which, for a given profile are all achieved from an homothety of the previous volumes.
The volume measurement unit is the cubic centimeter (cc).

Recapitulative tables for each implant type are found in the next pages :

B.III.3.1. IMGHC-LS-S : Smooth surface standard profile high cohesivity gel pre-filled breast implant :

CODE	SURFACE	PROFILE	VOLUME (cc)	DIAMETER (mm)	PROJECTION (mm)
IMGHC	SMOOTH	STANDARD	85	87	18
IMGHC	SMOOTH	STANDARD	105	92	20
IMGHC	SMOOTH	STANDARD	125	97	21
IMGHC	SMOOTH	STANDARD	145	102	23
IMGHC	SMOOTH	STANDARD	165	106	26
IMGHC	SMOOTH	STANDARD	185	108	27
IMGHC	SMOOTH	STANDARD	205	110	28
IMGHC	SMOOTH	STANDARD	225	114	29
IMGHC	SMOOTH	STANDARD	245	117	30
IMGHC	SMOOTH	STANDARD	265	124	31
IMGHC	SMOOTH	STANDARD	285	126	32
IMGHC	SMOOTH	STANDARD	305	128	33
IMGHC	SMOOTH	STANDARD	325	130	34
IMGHC	SMOOTH	STANDARD	345	132	35
IMGHC	SMOOTH	STANDARD	365	136	34
IMGHC	SMOOTH	STANDARD	415	141	35
IMGHC	SMOOTH	STANDARD	455	145	36
IMGHC	SMOOTH	STANDARD	505	150	37
IMGHC	SMOOTH	STANDARD	555	156	38
IMGHC	SMOOTH	STANDARD	605	160	39
IMGHC	SMOOTH	STANDARD	655	166	40
IMGHC	SMOOTH	STANDARD	705	172	41

B.III.3.2. IMGHC-LS-H : Smooth surface High profile High cohesivity gel pre-filled breast implants :

CODE	SURFACE	PROFILE	VOLUME (cc)	DIAMETER (mm)	PROJECTION (mm)
IMGHC	SMOOTH	HIGH	90	80	29
IMGHC	SMOOTH	HIGH	130	84	32
IMGHC	SMOOTH	HIGH	150	90	34
IMGHC	SMOOTH	HIGH	170	94	35
IMGHC	SMOOTH	HIGH	190	98	36
IMGHC	SMOOTH	HIGH	210	102	37
IMGHC	SMOOTH	HIGH	230	105	38
IMGHC	SMOOTH	HIGH	250	109	39
IMGHC	SMOOTH	HIGH	270	112	40
IMGHC	SMOOTH	HIGH	290	115	41
IMGHC	SMOOTH	HIGH	310	118	42
IMGHC	SMOOTH	HIGH	330	121	43
IMGHC	SMOOTH	HIGH	350	126	44
IMGHC	SMOOTH	HIGH	390	128	45
IMGHC	SMOOTH	HIGH	430	135	46
IMGHC	SMOOTH	HIGH	470	142	47
IMGHC	SMOOTH	HIGH	510	146	48
IMGHC	SMOOTH	HIGH	570	151	49
IMGHC	SMOOTH	HIGH	620	157	50
IMGHC	SMOOTH	HIGH	680	160	51

B.III.3.3. IMGHC-TX-S : Textured surface Standard profile High cohesivity gel pre-filled breast implants :

CODE	SURFACE	PROFILE	VOLUME (cc)	DIAMETER (mm)	PROJECTION (mm)
IMGHC	TEXTURED	STANDARD	85	87	18
IMGHC	TEXTURED	STANDARD	105	92	20
IMGHC	TEXTURED	STANDARD	125	97	21
IMGHC	TEXTURED	STANDARD	145	102	23
IMGHC	TEXTURED	STANDARD	165	106	26
IMGHC	TEXTURED	STANDARD	185	108	27
IMGHC	TEXTURED	STANDARD	205	110	28
IMGHC	TEXTURED	STANDARD	225	114	29
IMGHC	TEXTURED	STANDARD	245	117	30
IMGHC	TEXTURED	STANDARD	265	124	31
IMGHC	TEXTURED	STANDARD	285	126	32
IMGHC	TEXTURED	STANDARD	305	128	33
IMGHC	TEXTURED	STANDARD	325	130	34
IMGHC	TEXTURED	STANDARD	345	132	35
IMGHC	TEXTURED	STANDARD	365	136	34
IMGHC	TEXTURED	STANDARD	415	141	35
IMGHC	TEXTURED	STANDARD	455	145	36
IMGHC	TEXTURED	STANDARD	505	150	37
IMGHC	TEXTURED	STANDARD	555	156	38
IMGHC	TEXTURED	STANDARD	605	160	39
IMGHC	TEXTURED	STANDARD	655	166	40
IMGHC	TEXTURED	STANDARD	705	172	41

B.III.3.4. IMGHC-TX-H : Textured surface High profile High cohesivity gel pre-filled breast implants :

CODE	SURFACE	PROFILE	VOLUME (cc)	DIAMETER (mm)	PROJECTION (mm)
IMGHC	TEXTURED	HIGH	90	80	29
IMGHC	TEXTURED	HIGH	130	84	32
IMGHC	TEXTURED	HIGH	150	90	34
IMGHC	TEXTURED	HIGH	170	94	35
IMGHC	TEXTURED	HIGH	190	98	36
IMGHC	TEXTURED	HIGH	210	102	37
IMGHC	TEXTURED	HIGH	230	105	38
IMGHC	TEXTURED	HIGH	250	109	39
IMGHC	TEXTURED	HIGH	270	112	40
IMGHC	TEXTURED	HIGH	290	115	41
IMGHC	TEXTURED	HIGH	310	118	42
IMGHC	TEXTURED	HIGH	330	121	43
IMGHC	TEXTURED	HIGH	350	126	44
IMGHC	TEXTURED	HIGH	390	128	45
IMGHC	TEXTURED	HIGH	430	135	46
IMGHC	TEXTURED	HIGH	470	142	47
IMGHC	TEXTURED	HIGH	510	146	48
IMGHC	TEXTURED	HIGH	570	151	49
IMGHC	TEXTURED	HIGH	620	157	50
IMGHC	TEXTURED	HIGH	680	160	51

B.III.3.5. IMGHC-TX-R : Textured surface Reconstruction profile High cohesivity gel pre-filled breast implants :

CODE	SURFACE	PROFILE	VOLUME (cc)	LENGTH (mm)	WIDTH (mm)	PROJECTION (mm)
IMGHC	TEXTURED	RECONSTRUCTION	180	111	96	39
IMGHC	TEXTURED	RECONSTRUCTION	220	113	98	41
IMGHC	TEXTURED	RECONSTRUCTION	260	120	98	44
IMGHC	TEXTURED	RECONSTRUCTION	330	127	111	48
IMGHC	TEXTURED	RECONSTRUCTION	420	132	118	53
IMGHC	TEXTURED	RECONSTRUCTION	500	143	124	57
IMGHC	TEXTURED	RECONSTRUCTION	600	154	137	60

B.III.3.6. IMGHC-TX-AL : Textured surface Asymmetrical profile High cohesivity gel pre-filled breast implants - Left side :

CODE	SURFACE	PROFILE	VOLUME (cc)	LENGTH (mm)	WIDTH (mm)	PROJECTION (mm)
IMGHC	TEXTURED	ASYMMETRICAL	200	109	86	36
IMGHC	TEXTURED	ASYMMETRICAL	230	114	89	39
IMGHC	TEXTURED	ASYMMETRICAL	245	119	93	42
IMGHC	TEXTURED	ASYMMETRICAL	260	125	98	44
IMGHC	TEXTURED	ASYMMETRICAL	280	130	102	46
IMGHC	TEXTURED	ASYMMETRICAL	300	135	107	48
IMGHC	TEXTURED	ASYMMETRICAL	330	138	110	50
IMGHC	TEXTURED	ASYMMETRICAL	370	143	115	52
IMGHC	TEXTURED	ASYMMETRICAL	400	148	119	54
IMGHC	TEXTURED	ASYMMETRICAL	450	153	124	56

B.III.3.7. IMGHC-TX-AR : Textured surface Asymmetrical profile High cohesivity gel pre-filled breast implants - Right side :

CODE	SURFACE	PROFILE	VOLUME (cc)	LENGTH (mm)	WIDTH (mm)	PROJECTION (mm)
IMGHC	TEXTURED	ASYMMETRICAL	200	109	86	36
IMGHC	TEXTURED	ASYMMETRICAL	230	114	89	39
IMGHC	TEXTURED	ASYMMETRICAL	245	119	93	42
IMGHC	TEXTURED	ASYMMETRICAL	260	125	98	44
IMGHC	TEXTURED	ASYMMETRICAL	280	130	102	46
IMGHC	TEXTURED	ASYMMETRICAL	300	135	107	48
IMGHC	TEXTURED	ASYMMETRICAL	330	138	110	50
IMGHC	TEXTURED	ASYMMETRICAL	370	143	115	52
IMGHC	TEXTURED	ASYMMETRICAL	400	148	119	54
IMGHC	TEXTURED	ASYMMETRICAL	450	153	124	56

B.III.3.8. IMGHC-LS-EH : Smooth surface Extra High profile High cohesivity gel pre-filled breast implants :

CODE	SURFACE	PROFILE	VOLUME (cc)	DIAMETER (mm)	PROJECTION (mm)
IMGHC	SMOOTH	EXTRA-HIGH	115	79	36
IMGHC	SMOOTH	EXTRA-HIGH	135	83	38
IMGHC	SMOOTH	EXTRA-HIGH	165	88	41
IMGHC	SMOOTH	EXTRA-HIGH	195	91	43
IMGHC	SMOOTH	EXTRA-HIGH	215	96	44
IMGHC	SMOOTH	EXTRA-HIGH	245	99	45
IMGHC	SMOOTH	EXTRA-HIGH	265	104	46
IMGHC	SMOOTH	EXTRA-HIGH	285	106	47
IMGHC	SMOOTH	EXTRA-HIGH	305	109	48
IMGHC	SMOOTH	EXTRA-HIGH	335	112	49
IMGHC	SMOOTH	EXTRA-HIGH	365	115	52
IMGHC	SMOOTH	EXTRA-HIGH	395	119	53
IMGHC	SMOOTH	EXTRA-HIGH	445	123	54
IMGHC	SMOOTH	EXTRA-HIGH	475	126	56
IMGHC	SMOOTH	EXTRA-HIGH	515	130	58
IMGHC	SMOOTH	EXTRA-HIGH	555	134	59
IMGHC	SMOOTH	EXTRA-HIGH	615	138	60
IMGHC	SMOOTH	EXTRA-HIGH	705	142	66
IMGHC	SMOOTH	EXTRA-HIGH	755	146	67
IMGHC	SMOOTH	EXTRA-HIGH	805	149	70

B.III.3.9. IMGHC-TX-EH : TeXtured surface Extra High profile High cohesivity gel pre-filled breast implants :

CODE	SURFACE	PROFILE	VOLUME (cc)	DIAMETER (mm)	PROJECTION (mm)
IMGHC	TEXTURED	EXTRA-HIGH	115	79	36
IMGHC	TEXTURED	EXTRA-HIGH	135	83	38
IMGHC	TEXTURED	EXTRA-HIGH	165	88	41
IMGHC	TEXTURED	EXTRA-HIGH	195	91	43
IMGHC	TEXTURED	EXTRA-HIGH	215	96	44
IMGHC	TEXTURED	EXTRA-HIGH	245	99	45
IMGHC	TEXTURED	EXTRA-HIGH	265	104	46
IMGHC	TEXTURED	EXTRA-HIGH	285	106	47
IMGHC	TEXTURED	EXTRA-HIGH	305	109	48
IMGHC	TEXTURED	EXTRA-HIGH	335	112	49
IMGHC	TEXTURED	EXTRA-HIGH	365	115	52
IMGHC	TEXTURED	EXTRA-HIGH	395	119	53
IMGHC	TEXTURED	EXTRA-HIGH	445	123	54
IMGHC	TEXTURED	EXTRA-HIGH	475	126	56
IMGHC	TEXTURED	EXTRA-HIGH	515	130	58
IMGHC	TEXTURED	EXTRA-HIGH	555	134	59
IMGHC	TEXTURED	EXTRA-HIGH	615	138	60
IMGHC	TEXTURED	EXTRA-HIGH	705	142	66
IMGHC	TEXTURED	EXTRA-HIGH	755	146	67
IMGHC	TEXTURED	EXTRA-HIGH	805	149	70

C. Materials

C.I. Materials :

C.I.1. Finished product definition :

A high cohesivity silicone gel pre-filled breast implant is made of the following elements :

- a silicone elastomer envelope (smooth or textured),
- a closure patch in silicone elastomer which closes the hole left by the mold handle when removing the envelope from the mold,
- a very first gluing layer in silicone elastomer on the envelope at the gluing surface with the closure patch level
- a very first gluing layer in silicone elastomer on the closure patch
- a silicone elastomer to glue the closure patch on the envelope,
- a filling product, the high cohesivity silicone gel,
- a silicone elastomer to close the filling hole.

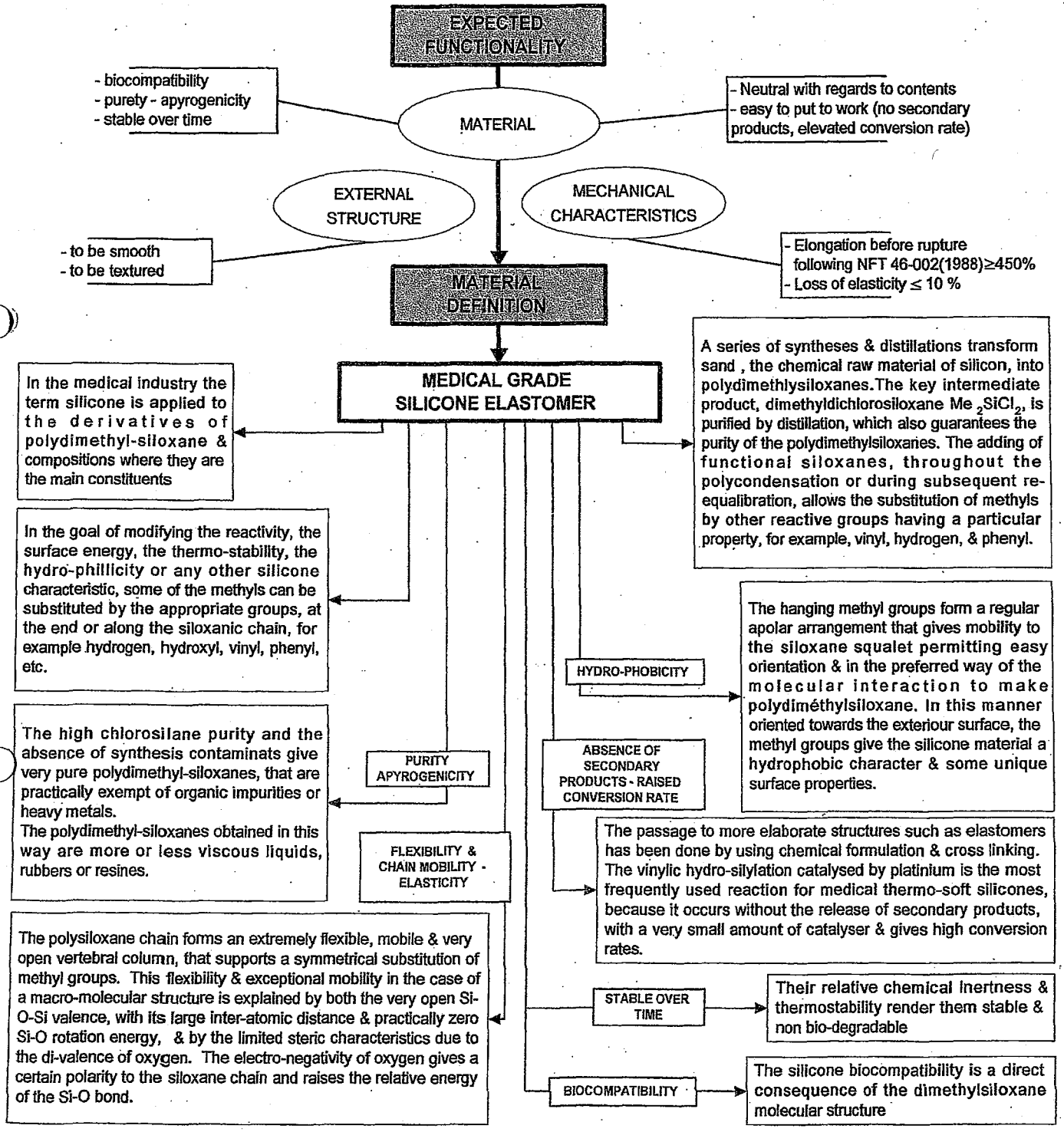
Asymmetrical and reconstruction profiles have a tactile and visual location system on their textured envelope:

- 3 points in relief, in silicone elastomer, on the closure and finishing patch side
- absence of texturing elements on a 2 mm x 4 cm little strip on the opposite side of the closure and finishing patches.

All the design elements for each elements are gathered in the following paragraphs.

C.I.1.1. Envelope :

a) General definition :



b) Raw material choice :

Silicone type : Polydimethyldiphenylsiloxane – medical grade silicone
Smooth envelope : NUSIL MED6 6400 (4 layers)
Textured envelope : NUSIL MED6 6400 (4 layers) + NUSIL MED26 6400 (last layer)

The technical specifications of the MED6 6400 are described in the form *[see Annex Cl.34]*

c) Raw material biocompatibility – MED6 6400 :

The following tests were performed to evaluate biocompatibility on the raw materials and implemented by NAmSA for Nusil. *(NamSA : 9 Morgan Irvine – CA 92718)*

➢ ***Cytotoxicity***
[see Annex Cl.1]

The methodology used complies with the GLP (21 CFR 58).
Some material extracts are performed with some culture medium for cells and put in contact with mouse fibroblasts. The material is not cytotoxical.

➢ ***In vitro hemolysis***
[see Annex Cl.2]

The methodology used complies with the GLP (21 CFR 58).
Some material extracts are performed in some sodium chloride and put in contact with rabbit blood.
The material is not haemolytical.

➢ ***Toxicity by systemic injection***
[see Annex Cl.3]

The methodology used complies with the GLP (21 CFR 58) and the USP guidelines. Some material extracts are performed with some sodium chloride (SC) and cotton seed oil (CSO). They are then injected in mice by intraveinous route (SC) and by intraperitoneal route 5CSO). Animals are regularly observed until 72 hours. No mortality occurred and there is no systemic toxicity sign.

➢ ***Intradermic injection in the rabbit***
[see Annex Cl.4]

The methodology used complies with the GLP (21 CFR 58) and the USP guidelines. Some material extracts are performed with sodium chloride (SC) and cotton seed oil (CSO). They are injected to rabbits in intraccutaneous. Animals are regularly observed until 72 hours to detect erythema and oedema. There is no irritation or toxicity sign.

➢ ***Implantation in the rabbit***

[see Annex Cl.5]

The methodology used complies with the GLP (21 CFR 58) and the USP guidelines. The testing material is implanted in the muscle, in the rabbit. After 90 days, animals are submitted to euthanasia and the implantation sites are analyzed, histological examinations are performed. The implantation didn't provoke any significant macroscopic reaction and the implant was classified as non irritating from a microscopic point of view.

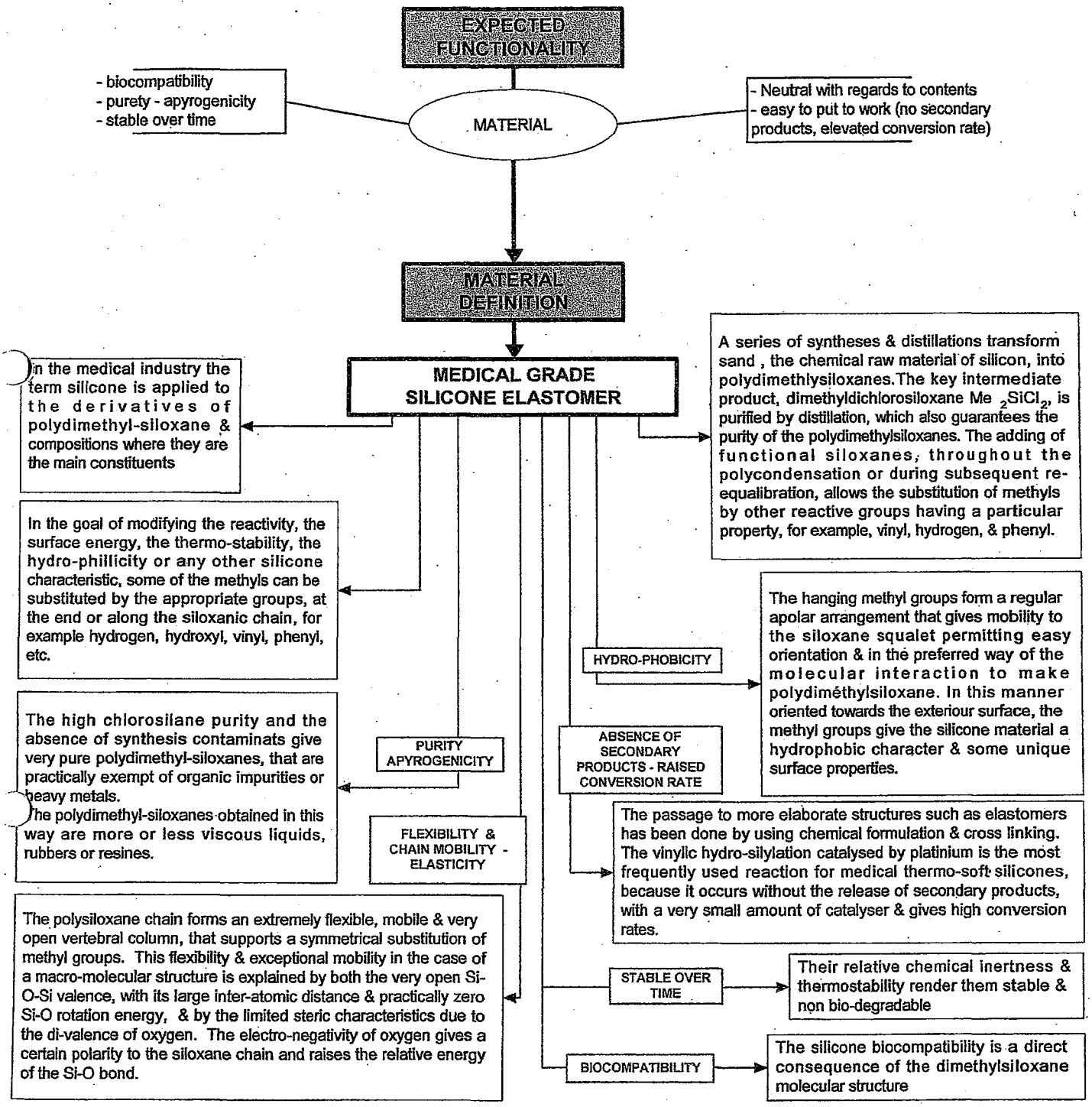
➢ ***Mutagenicity – Ames Test***

[see Annex Cl.6]

The methodology used is that of Ames and al. and complies with the GLP (21 CFR 58). Some material extracts are performed with some sodium chlorid (SC) and put in contact with the various Salmonella thyphimurium strains. The extracts are not mutagenic.

C.I.1.2. Closure patch :

a) General definition :



b) Raw material choice :

Silicone type : Polydimethyldiphenylsiloxane – medical grade silicone
Closure patch : NUSIL MED6 6400

The technical specifications of the MED6 6400 are described in the form *[see Annex Cl.34]*

c) Raw material biocompatibility – MED6 6400 :

The following tests were performed to evaluate biocompatibility on the raw material and implemented by NamSA for Nusil. *(NamSA : 9 Morgan Irvine – CA 92718)*

➢ ***Cytotoxicity***
[see Annex Cl.1]

The methodology used complies with the GLP (21 CFR 58).
Some material extracts are performed with some culture medium for cells and put in contact with mouse fibroblasts. The material is not cytotoxical.

➢ ***In vitro hemolysis***
[see Annex Cl.2]

The methodology used complies with the GLP (21 CFR 58).
Some material extracts are performed in some sodium chloride and put in contact with rabbit blood.
The material is not haemolytical.

➢ ***Toxicity by systemic injection***
[see Annex Cl.3]

The methodology used complies with the GLP (21 CFR 58) and the USP guidelines. Some material extracts are performed with some sodium chloride (SC) and cotton seed oil (CSO). They are then injected in mice by intraveinous route (SC) and by intraperitoneal route (CSO). Animals are regularly observed until 72 hours. No mortality occurred and there is no systemic toxicity sign.

➢ ***Intradermic injection in the rabbit***
[see Annex Cl.4]

The methodology used complies with the GLP (21 CFR 58) and the USP guidelines. Some material extracts are performed with sodium chloride (SC) and cotton seed oil (CSO). They are injected to rabbits in intraccutaneous. Animals are regularly observed until 72 hours to detect erythema and oedema. There is no irritation or toxicity sign.

➢ ***Implantation in the rabbit***

[see Annex Cl.5]

The methodology used complies with the GLP (21 CFR 58) and the USP guidelines. The testing material is implanted in the muscle, in the rabbit. After 90 days, animals are submitted to euthanasia and the implantation sites are analyzed, histo logical examinations are performed. The implantation didn't provoke any significant macroscopic reaction and the implant was classified as non irritating from a microscopic point of view.

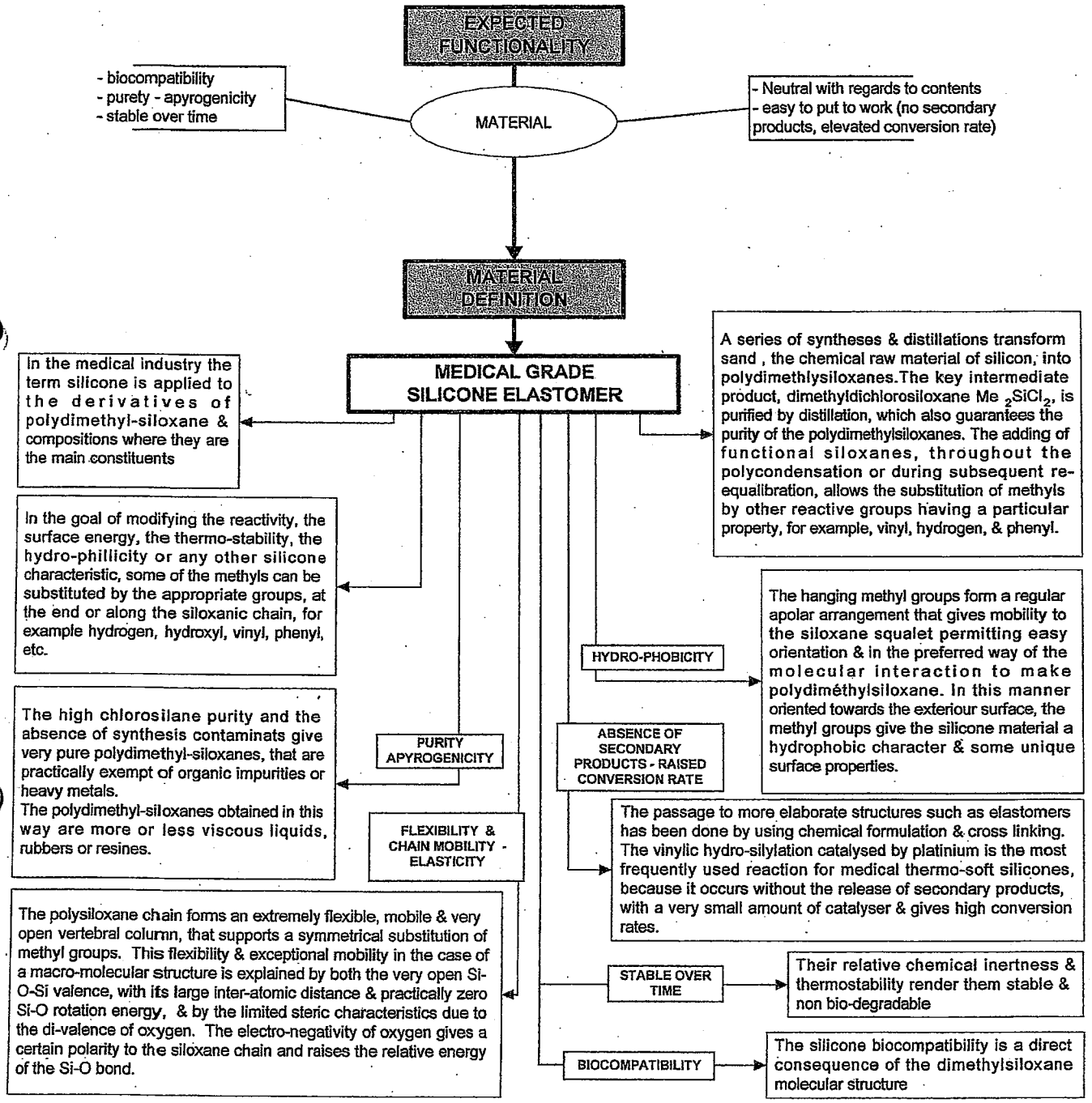
➢ ***Mutagenicity – Ames Test***

[see Annex Cl.6]

The methodology used is that of Ames and al. and complies with the GLP (21 CFR 58). Some material extracts are performed with some sodium chloride (SC) and put in contact with the various Salmonella thyphimurium strains. The extracts are not mutagenic.

C.I.1.3. Very first gluing layer on the envelope :

a) General definition :



b) Raw material choice :

Silicone type : Polydimethylmethylvinylsiloxane – medical grade silicone
Very first glue layer: NUSIL MED 6640

The technical specifications of the MED 6640 are described in the form *[see Annex Cl.35]*

c) Raw material biocompatibility – MED 6640 :

The following tests were performed to evaluate biocompatibility on the MED2 6640 and remain valid on the MED 6640. They were implemented by NamSA for Nusil.
(NamSA : 9 Morgan Irvine – CA 92718)

➢ ***Cytotoxicity***
[see Annex Cl.7]

Several in vitro biocompatibility tests were performed on the mouse. None of them could emphasize toxicity on the fibrosplaste cells of the mouse.

➢ ***In vitro hemolysis***
[see Annex Cl.8]

The In vitro hemolysis test by extraction in the sodium chloride show that the extracts considered are not hemolitic.

➢ ***Toxicity by systemic injection***
[see Annex Cl.9]

The systemic toxicity test by extraction in the sodium chloride were performed in the mouse. The extracts considered didn't lead to any mortality and the systemic toxicity was not emphasized by these tests.

➢ ***Intradermic injection in the rabbit***
[see Annex Cl.10]

The toxicity test by intradermic injection in the rabbit were performed by extraction in the sodium chloride. The extracts didn't lead to any irritation and no toxicity was observed.

➢ ***Implantation in the rabbit***

[see Annex Cl.11]

The implantation didn't lead to any significant macroscopic reaction and the implant was classified as "no irritating" from a microscopical point of view.

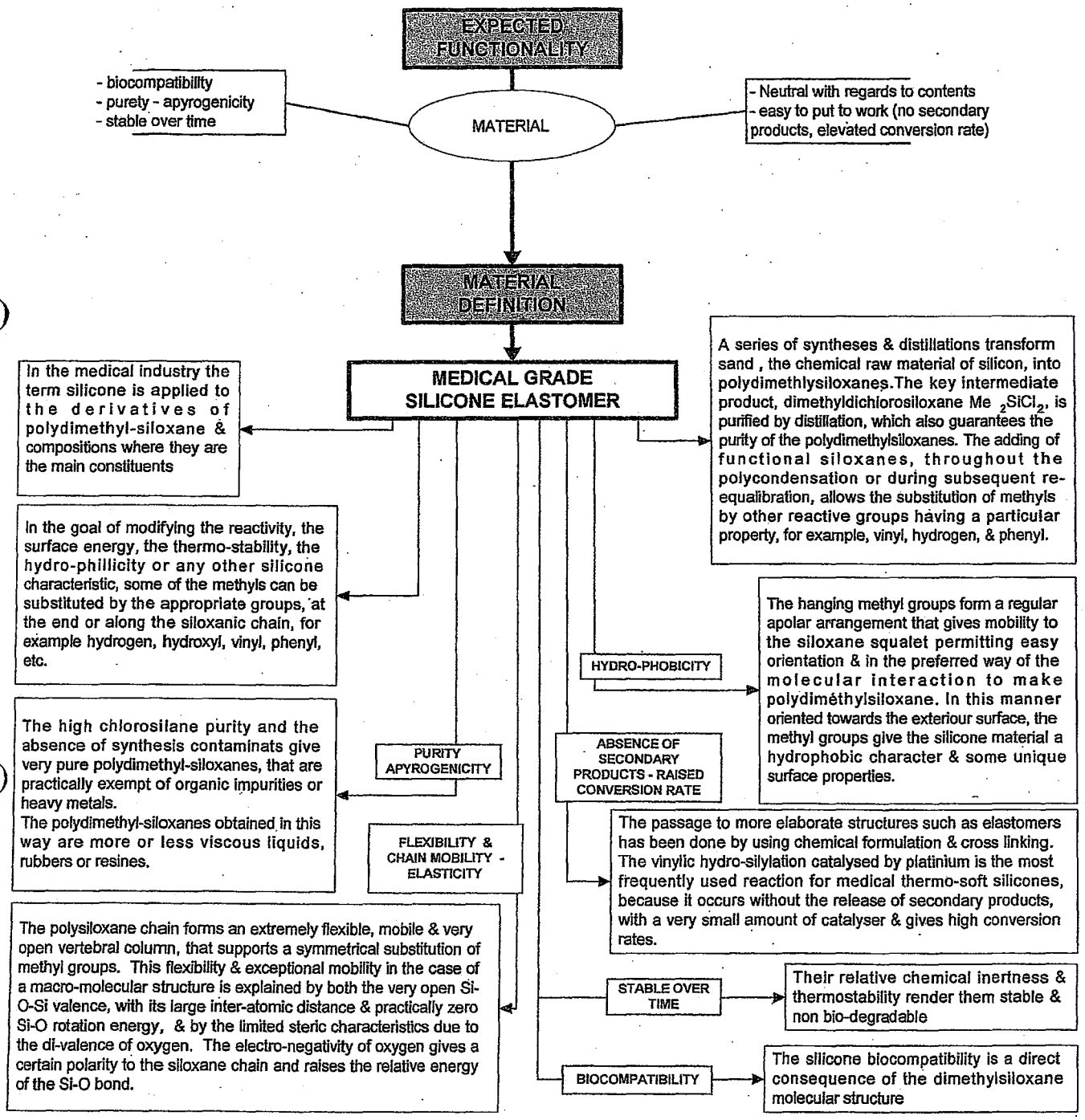
➢ ***Mutagenicity – Ames Test***

[see Annex Cl.12]

The mutagenicity tests by extraction in the sodium chloride showed that the extracts don't induce mutagenic changes in the salmonella typhimurium.

C.I.1.4. Glue :

a) General definition :



b) Raw material choice :

Silicone type : Polydimethylmethylvinylsiloxane – medical grade silicone
Glue : NUSIL MED 2245

The technical specifications of the MED 2245 are described in the form *[see Annex Cl.36]*

c) Raw material biocompatibility – MED 2245 :

The following tests were performed to evaluate biocompatibility on the raw material and implemented by NamSA for Nusil. *(NamSA : 9 Morgan Irvine – CA 92718)*

➢ ***Cytotoxicity***
[see Annex Cl.13]

Several in vitro cytotoxicity tests were performed on the mouse. None of them could emphasize toxicity on the fibrosplaste cells of the mouse.

➢ ***Toxicity by systemic injection***
[see Annex Cl.14]

The systemic toxicity test by extraction in the sodium chloride were performed in the mouse. The extracts considered didn't lead to any mortality and the systemic toxicity was not emphasized by these tests.

➢ ***Intradermic injection in the rabbit***
[see Annex Cl.15]

The toxicity test by intradermic injection in the rabbit were performed by extraction in the sodium chloride. The extracts didn't lead to any irritation and no toxicity was observed.

➢ ***Implantation in the rabbit***
[see Annex Cl.16]

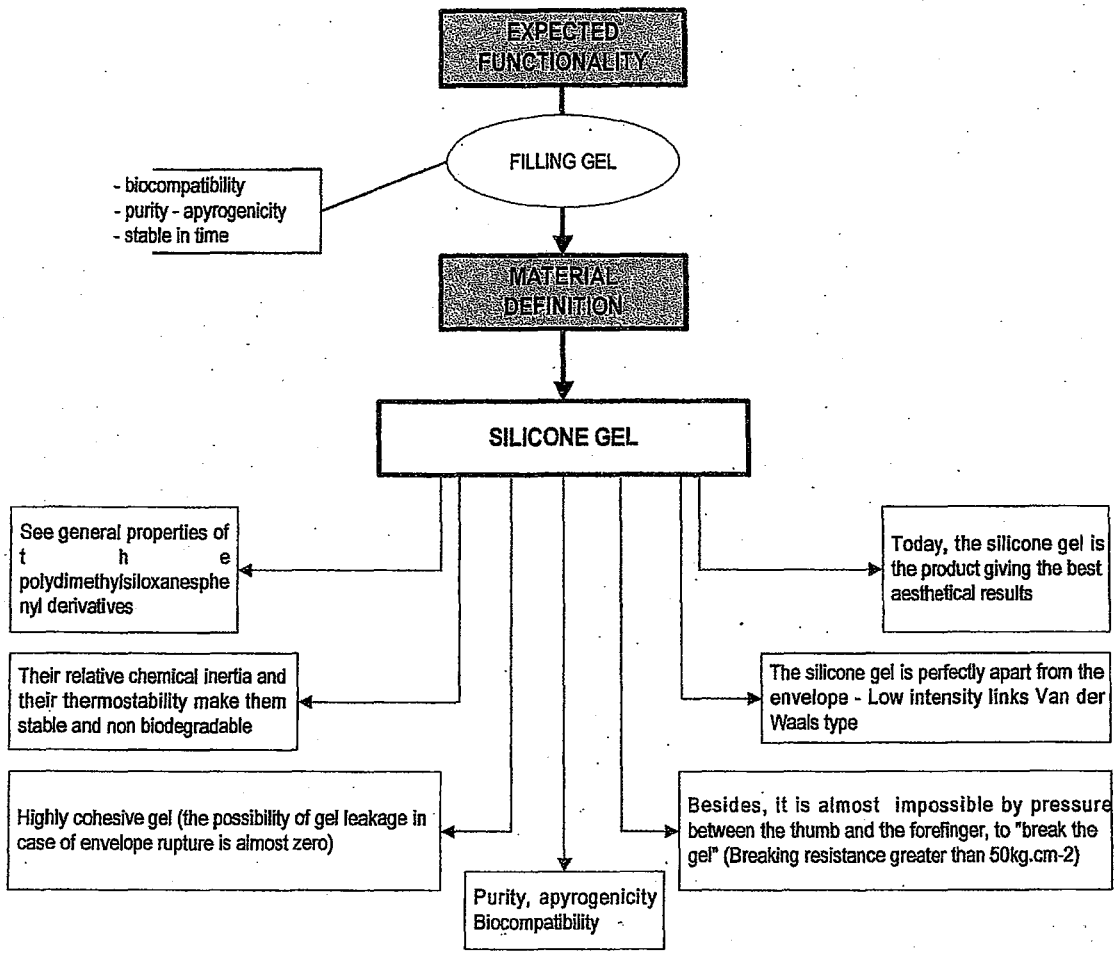
The implantation didn't lead to any significant macroscopic reaction and the implant was classified as "no irritating" from a microscopical point of view.

➢ ***Mutagenicity – Ames Test***
[see Annex Cl.17]

The mutagenicity tests by extraction in the sodium chloride showed that the extracts don't induce mutagenic changes in the salmonella typhimurium.

C.I.1.5. Filler material :

a) General definition :



b) Raw material choice :

Silicone type : Polydimethylmethylvinylsiloxane – medical grade silicone
Filler material : NUSIL MED3 6300

The technical specifications of the MED3 6300 are described in the form *[see Annex Cl.37]*

c) Raw material biocompatibility – MED3 6300 :

The following tests were performed to evaluate biocompatibility on the raw material and implemented by NamSA for Nusil. *(NamSA : 9 Morgan Irvine – CA 92718)*

➢ ***Cytotoxicity***
[see Annex Cl.18]

The methodologies used comply with the GLP (21 CFR 58) and the ISO 10993-5(1994) Standard.
Methodology in agarose :
The silicone gel is put in contact with the L-929 cells (mouse fibroblasts). After 24-hour incubation, the cells are observed with the microscope so as to detect any distortion, degeneration, detachment or cellular lysis. The material is not cytotoxic.
Methodology by extraction :
Some material extracts are performed with some culture medium for cells and put in contact with some mouse fibroblasts L-929. The cells are incubated for 48 hours. The material is not cytotoxic.

➢ ***In vitro hemolysis***
[see Annex Cl.19]

The methodology used complies with the GLP (21 CFR 58).
Some material extracts are performed in some sodium chloride (SC) and put in contact with some rabbit blood. The material is not haemolytical.

➢ ***Acute toxicity in the mouse***
[see Annex Cl.20]

The methodology used is in compliance with the GLP (21 CFR 58) and the ISO 10993-11(1996).
Some material extracts are performed with some sodium chloride (SC), an alcoholized saline solution (AS), glycol polyethylene (PEG) and cotton seed oil (CSO). They are injected in mice by intraveinous route (SC) and (AS) and by intraperitoneal route (PEG) and (CSO). Animals are regularly observed until 72 hours. No mortality occurred and there are no systemic toxicity signs.

➢ ***Intradermic injection in the rabbit***

[see Annex Cl.21]

The intra-cutaneous reactivity test was performed according to the ISO 10993-10(1996) Standard.
Some material extracts are performed with some sodium chloride (SC), an alcoholized saline solution (AS), glycol polyethylene (PEG) and cotton seed oil (CSO). They are injected to rabbits by the intra-cutaneous route. Animals are regularly observed until 72 hours to detect erythema and oedemas.There is no irritation or toxicity sign.

➢ ***Implantation in the muscle in the rabbit (7 and 90 days)***

[see Annex Cl.22]

The implantation test (1 week and 30 weeks) in the muscle was performed according to the ISO 10993-6(1995) Standard.
The testing material is implanted in the muscle in the rabbit.
Animals are submitted to euthanasia and the implantation sites are analyzed, histological examinations are performed. At 1 week, the implantation didn't provoke any significant macroscopic reaction and the implant was classified as slightly irritating from a microscopic point of view. At 30 weeks, the implantation didn't provoke any significant macroscopic reaction and the implant was classified as non irritating from a microscopical point of view

➢ ***Mutagenicity – Ames Test***

[see Annex Cl.23]

The methodology used is that of Ames and al. and complies with the GLP (21 CFR 58).
Some material extracts are performed with some sodium chloride (SC) and DMSO and are put in contact with various strains of Salmonella thyphimurium. Tests are performed with and without metabolic activation (S9 fraction). The silicone gel extracts are not mutagenic.

➢ ***Pyrogenicity test in the rabbit***

[see Annex Cl.24]

The pyrogenicity test was performed according to the ISO 10993-11(1996) Standard.
A silicone gel extract was performed with some sodium chloride (SC) and injected to rabbits by intraveinous route. The rabbit temperature is regularly measured out for the 3 hours following the injection.
The silicone gel is declared non pyrogenic.

➢ ***Cutaneous irritation in the rabbit***

[see Annex Cl.25]

The cutaneous irritation test was performed according to the ISO 10993-10(1996) Standard. The silicone gel is directly applied on the rabbit skin. The exposed sites are regularly observed (until 72 hours after gel withdrawal) to detect any sign of erythema or oedema.
The silicone gel is declared as non irritating.

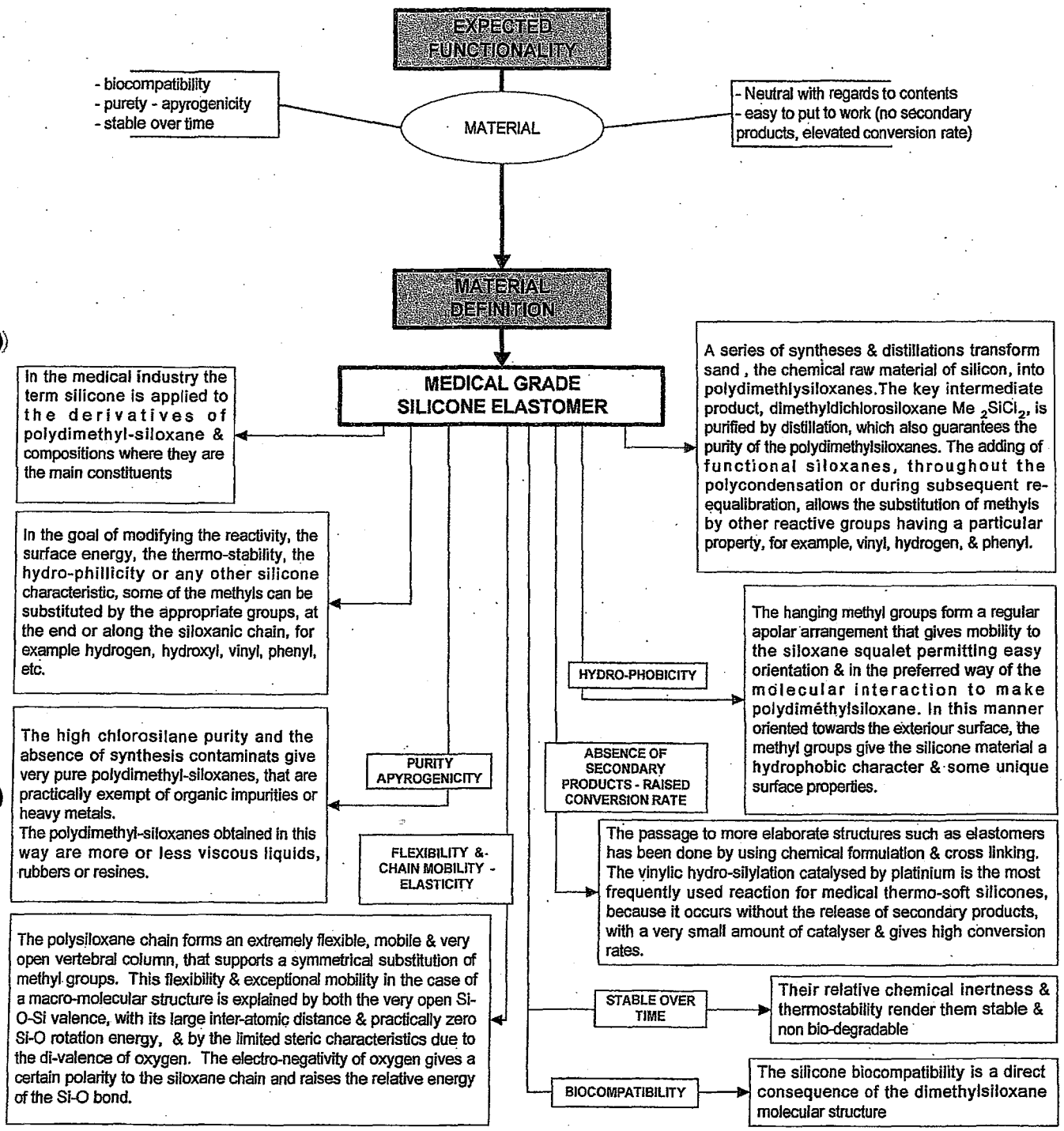
➢ ***Sensitization test in the guinea pig***

[see Annex Cl.26]

The sensitization test was performed according to the ISO 10993-10(1996) Standard.
The silicone gel extracts are performed with some sodium chloride (SC) and cotton seed oil (CSO).
Induction I : the extracts are injected by intradermal route in the guinea pig
Induction II : At D6, injections are performed again on the same site as the first induction and 24 hours after the occlusive dressing containing the extract for a 48 hour time.
Test : 15 days after, occluded topical applications of the extract are performed on a never treated zone.
The sensitization reaction is evaluated noting down the erythema and oedema. The silicone gel is not sensitizing.

C.I.1.6. Closure solution :

a) General definition :



b) Raw material choice :

Silicone type : Organopolysiloxane RTV – medical grade silicone elastomer
Closure solution : APPLIED SILICONE PN 40076

The technical specifications of the PN 40 076 are described in the form *[see Annex Cl.38]*

c) Raw material biocompatibility – PN 40076 :

The following biocompatibility tests were performed for « Applied Silicone Corporation »(320 W.Stanley Avenue Ventura - CA 93001) by NamSA et UBTL companies :

NamSA – 9 morgan Irvine, CA 92 718
UBTL, Inc – 520 Wakara Way – Salt Lake City, Utah 84108

➢ ***Cytotoxicity***
[see Annex Cl.27]

Cytotoxicity tests were performed in the mouse fibroblast cells from the material extracts (in some culture medium for cells). No cytotoxicity sign was observed.

➢ ***Intradermal irritation***
[see Annex Cl.28]

Some material extracts were performed in sodium chloride at 0.9% (SC) and cotton seed oil (CSO). The extracts are injected in subcutaneous in rabbits. Under the testing conditions, no toxicity or irritation sign was observed.

➢ ***Systemic toxicity***
[see Annex Cl.29]

The systemic toxicity test was performed in compliance with the USP guidelines. Some material extracts are injected in the sodium chloride (SC) and in the cotton seed oil (CSO). The extracts are injected by intraveinous (SC) and intraperitoneal (CSO) route in mice. No mortality or systemic toxicity signs were observed.

➢ ***Implantation***
[see Annex Cl.30]

The implantation test in the muscle was performed in compliance with the USP guidelines. The elastomer was implanted in the rabbit for 90 days. After the animal sacrifice, macroscopic and microscopic (histopathologic) observations of the implantation site were observed. The implantation didn't provoke significant macroscopic reaction and the implant was classified as "non irritating" from a microscopic point of view.

➢ ***Chronic toxicity***

[see Annex Cl.31]

A chronic toxicity study was performed implanting in subcutaneous in the rat the elastomer to test. No systemic toxicity (body weight, organ weight, haematology, biochemical analyses...) was noticed.

➢ ***Genotoxicity***

[see Annex Cl.32]

Some material extracts are performed in the sodium chloride and DMSO, and the evaluation of their mutagenic power is tested, in presence and absence of metabolic activation (S9). The extracts don't induce mutagen changes in the various strains of tested Salmonella typhimurium.

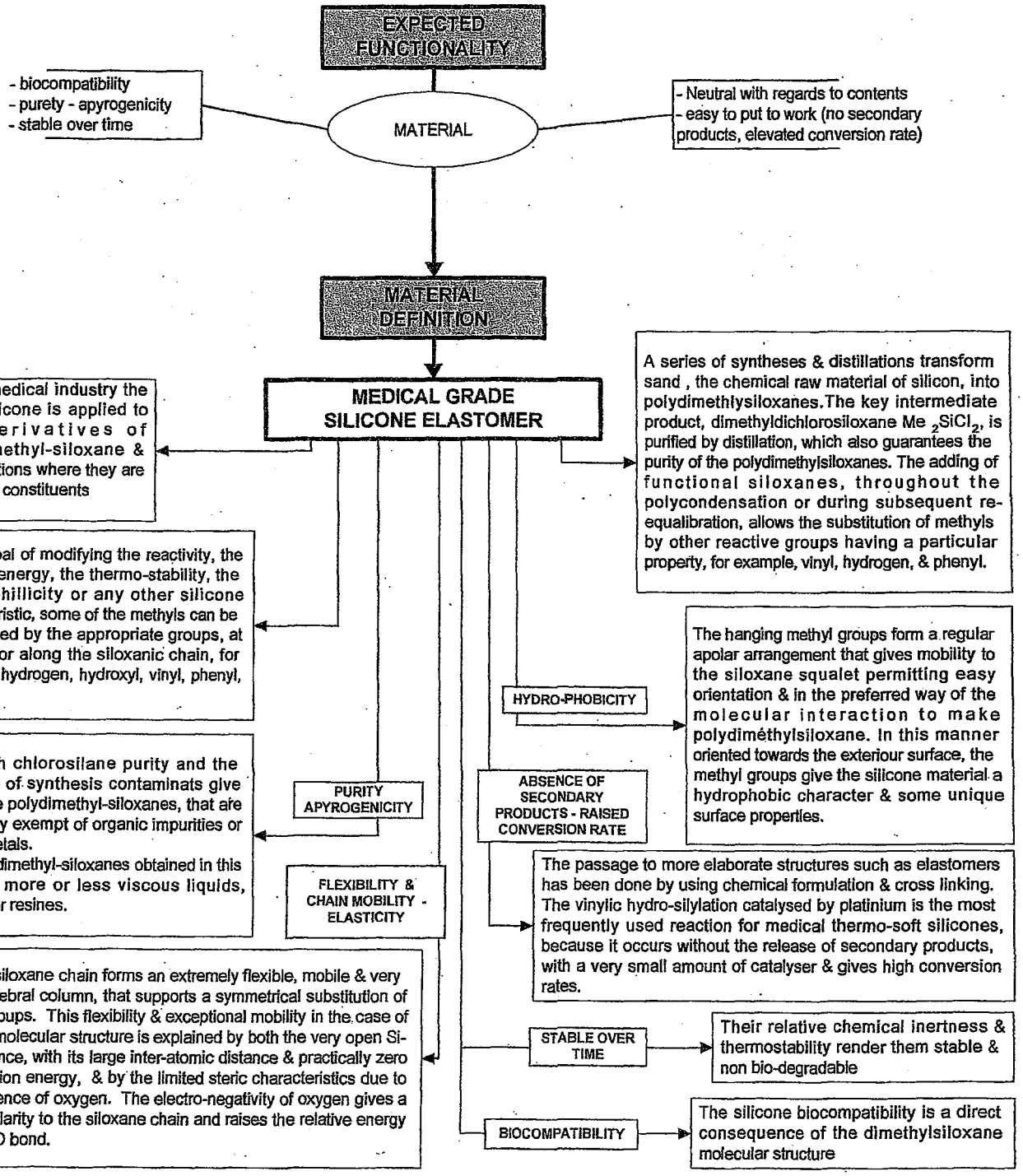
➢ ***Reprocdutive effects***

[see Annex Cl.33]

A reproductive toxicity test was performed after implanting the elastomer in subcutaneous in female rats. After gestation, the foetus study didn't show any teratogenic effects.

C.I.1.7. Finishing patch :

a) General definition :



b) Raw material choice :

Silicone type : Polydimethyldiphenylsiloxan – médical grade silicone elastomer
Finishing patch : NUSIL MED6 6400

The technical specifications of the MED6 6400 are described in the form *[see Annex Cl.34]*

c) Raw material biocompatibility – MED6 6400 :

The following biocompatibility tests were performed to evaluate biocompatibility on the raw material and performed by NamSA for Nusil (NamSa : 9 Morgan Irvine – CA 92718)

➢ ***Cytotoxicity***
[see Annex Cl.1]

The methodology used complies with the GLP (21 CFR 58).
Some material extracts are performed with some culture medium for cells and put in contact with mouse fibroblasts. The material is not cytotoxical.

➢ ***In vitro hemolysis***
[see Annex Cl.2]

The methodology used complies with the GLP (21 CFR 58).
Some material extracts are performed in some sodium chloride and put in contact with rabbit blood.
The material is not haemolytical.

➢ ***Toxicity by systemic injection***
[see Annex Cl.3]

The methodology used complies with the GLP (21 CFR 58) and the USP guidelines. Some material extracts are performed with some sodium chloride (SC) and cotton seed oil (CSO). They are then injected in mice by intraveinous route (SC) and by intraperitoneal route (CSO). Animals are regularly observed until 72 hours. No mortality occurred and there is no systemic toxicity sign.

➢ ***Intradermic injection in the rabbit***
[see Annex Cl.4]

The methodology used complies with the GLP (21 CFR 58) and the USP guidelines. Some material extracts are performed with sodium chloride (SC) and cotton seed oil (CSO). They are injected to rabbits in intra cutaneous. Animals are regularly observed until 72 hours to detect erythema and oedema. There is no irritation or toxicity sign.

➢ ***Implantation in the rabbit***

[see Annex Cl.5]

The methodology used complies with the GLP (21 CFR 58) and the USP guidelines. The testing material is implanted in the muscle, in the rabbit. After 90 days, animals are submitted to euthanasia and the implantation sites are analyzed, histo logical examinations are performed. The implantation didn't provoke any significant macroscopic reaction and the implant was classified as non irritating from a microscopic point of view.

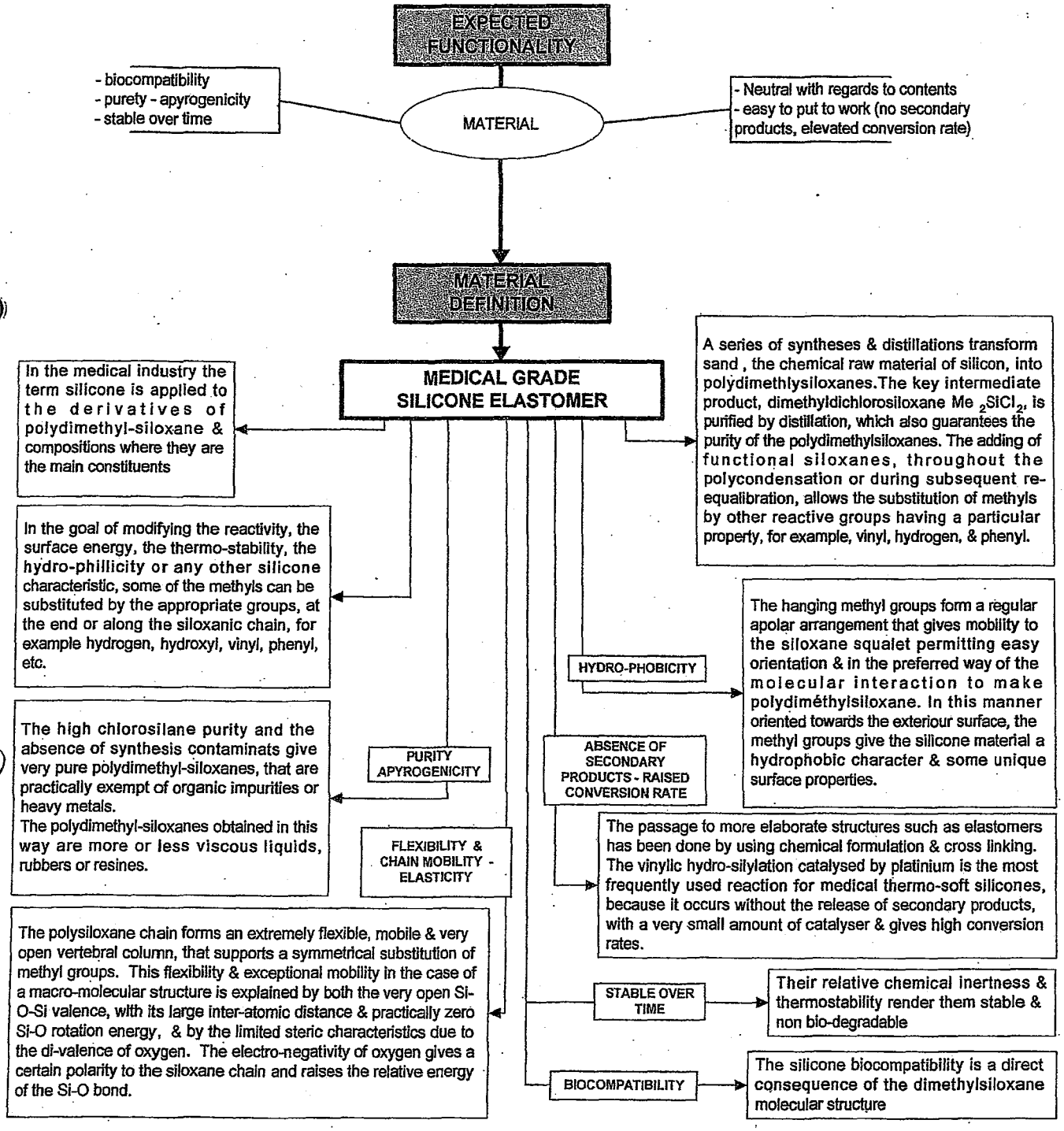
➢ ***Mutagenicity – Ames Test***

[see Annex Cl.6]

The methodology used is that of Ames and al. and complies with the GLP (21 CFR 58). Some material extracts are performed with some sodium chloride (SC) and put in contact with the various Salmonella thyphimurium strains. The extracts are not mutagenic.

C.I.1.8. Tactile location system : points in relief for Asymmetrical and Reconstruction profiles :

a) General definition :



b) Raw material choice :

Silicone type : Organopolysiloxane RTV – medical grade silicone elastomer
Points in relief : APPLIED SILICONE PN 40076

The technical specifications of the PN 40 076 are described in the form *[see Annex Cl.38]*

c) Raw material biocompatibility – PN 40076 :

The following biocompatibility tests were performed for « Applied Silicone Corporation »(320 W.Stanley Avenue Ventura - CA 93001) by NamSA and UBTL companies :

NamSA – 9 morgan Irvine, CA 92 718
UBTL, Inc – 520 Wakara Way – Salt Lake City, Utah 84108

➢ ***Cytotoxicity***
[see Annex Cl.27]

Cytotoxicity tests were performed in the mouse fibroblast cells from the material extracts (in some culture medium for cells). No cytotoxicity sign was observed.

➢ ***Intradermal irritation***
[see Annex Cl.28]

Some material extracts were performed in sodium chloride at 0.9% (SC) and cotton seed oil (CSO). The extracts are injected in subcutaneous in rabbits. Under the testing conditions, no toxicity or irritation sign was observed.

➢ ***Systemic toxicity***
[see Annex Cl.29]

The systemic toxicity test was performed in compliance with the USP guidelines. Some material extracts are injected in the sodium chloride (SC) and in the cotton seed oil (CSO). The extracts are injected by intraveinous (SC) and intraperitoneal (CSO) route in mice. No mortality or systemic toxicity signs were observed.

➢ ***Implantation***
[see Annex Cl.30]

The implantation test in the muscle was performed in compliance with the USP guidelines. The elastomer was implanted in the rabbit for 90 days. After the animal sacrifice, macroscopic and microscopic (histopathologic) observations of the implantation site were observed. The implantation didn't provoke significant macroscopic reaction and the implant was classified as "non irritating" from a microscopic point of view.

➢ ***Chronic toxicity***

[see Annex CI.31]

A chronic toxicity study was performed implanting in subcutaneous in the rat the elastomer to test. No systemic toxicity (body weight, organ weight, haematology, biochemical analyses...) was noticed.

➢ ***Genotoxicity***

[see Annex CI.32]

Some material extracts are performed in the sodium chloride and DMSO, and the evaluation of their mutagenic power is tested, in presence and absence of metabolic activation (S9). The extracts don't induce mutagen changes in the various strains of tested Salmonella typhimurium.

➢ ***Reproductive effects***

[see Annex CI.33]

A reproductive toxicity test was performed after implanting the elastomer in subcutaneous in female rats. After gestation, the foetus study didn't show any teratogenic effects.

C.I.1.9. Visual location system : absence of texturing elements for Asymmetrical and Reconstruction profiles:

The absence of texture is achieved by applying a teflon little strip (40 mm x 2 mm) prior to the texture phase. This strip, non adhering is then removed leaving a smooth trace having the features of the smooth envelope, described in section C.I.1.1.

The Teflon technical specifications are described in the form *[see Annex CI.34]*

C.I.2. Additives :

These are the solvents, the cleaning products or any other additives used in-process. An analysis (see section D.III.3) allows verifying they are no longer present in the finished product or the content is lower than the acceptable limit of leachable substances in the human body established in the scope of the ISO/DIS 10993-17.2 (1999) Standard : *Biological evaluation of medical devices – Part 17 : Methods for establishing acceptable limits of leachable substances using the health-related risk evaluation.*

C.I.2.1. Xylene :

- xylene is the dispersion agent of medical grade silicones supplied by Nusil company : the MED6 6400 used to manufacture the envelope, closure and finishing patches and the MED 6640 used as very first gluing layer.

- some xylene bought by P.I.P. can also be added to adjust viscosity at the time of the dipping and texture phases. This product specifications are defined in the form *[see Annex CI.40]*

C.I.2.2. Heptane :

Heptane is used to adjust viscosity when manufacturing closure and finishing patches and to dissolve the glue. This product technical specifications are defined in the form *[see Annex CI.41]*

C.I.2.3. Ethanol :

Ethanol is used to clean the smooth envelopes after the mold removal. This product technical specifications are defined in the form *[see Annex CI.42]*

C.I.2.4. Isopropylic alcohol :

Isopropylic alcohol is used to clean the stamped finishing patches. This product technical specifications are defined in the form *[see Annex CI.43]*

C.I.2.5. Texturing agent :

The texturing agent is the calibrated saccharine used during the envelope texturing phase. This product technical specifications are defined in the form *[see Annex CI.44]*

C.I.2.6. Hydrogen peroxide 10 volumes :

The hydrogen peroxide 10 volumes (aqueous solution at 3% hydrogen peroxide) is used at the finished product washing step prior to the final sterilization. This product technical specifications are defined in the form *[see Annex CI.45]*

C.II. Labelling :

Labels were defined in compliance with the essential requirements given in Appendix I of the European Directive 93/42 EEC and with the specific prescriptions of the NF EN 1041(1998) and the NF EN 980(1996) Standards.

The labelling is made of an identification label and three self-adhesive labels stuck to the using unit and visible through the protected unit.

See Annex CII.1 : IMGHC-TX CE labelling
IMGHC-LS CE labelling

C.II.1. Identification label :

The label is stuck to the external cover in TYVEK and helps know

- The manufacturer name and location,
- The implant type,
- The implant dimensions (profile, volume, diameter, projection)
- The implant lot and serial numbers,
- The implant code,
- The expiry date,
- The symbol « SINGLE USE »,
- The symbol « ETHYLENE OXIDE STERILIZED »,
- the mention « DO NOT RE-STERILIZE »,
- the indication to resort to the instructions for use to the attention of patients and surgeons for additional information,
- the indication to verify the sterility protector integrity,
- the storage conditions,
- the CE mark.

C.II.2. Self-adhesive labels :

They are three and also stuck to the external cover. They are filled in at the time of surgery with :

- the patient name, the surgeon name
- the implantation date,
- the implantation side (left or right),
- the possible observations,
- the implant references.

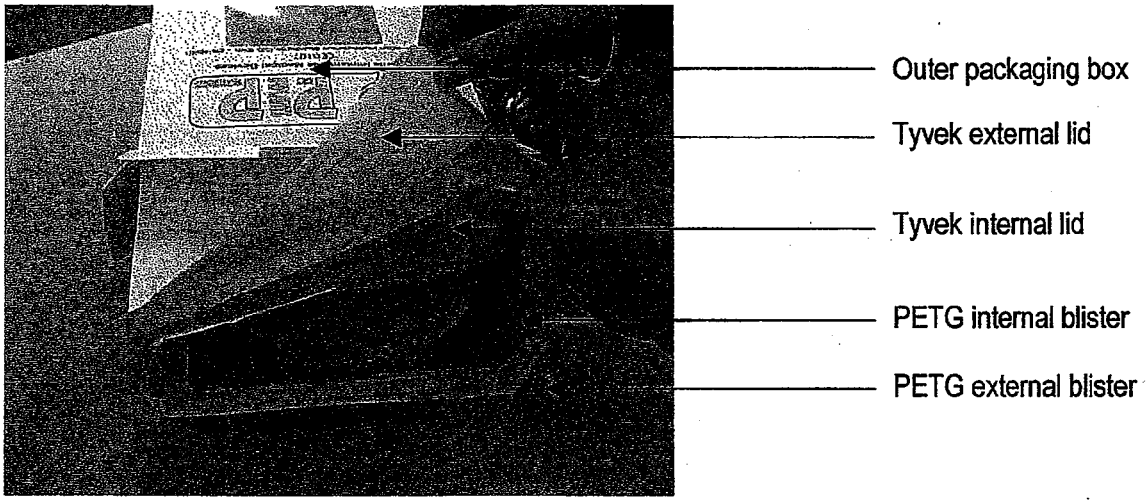
C.III. Packaging :

Silicone gel pre-filled breast implants are packed, per unit, in a Blister type packaging, which, according to its performances, allows keeping the implant integrity and sterility.

C.III.1. Packaging presentation :

The packaging is made of the following elements :

⇨ an « internal » blister in PETG adapted to the implant shape, sealed with a Tyvek « internal » lid
⇨ an « external » blister in PETG of standard shape, sealed with a Tyvek « external » lid
⇨ an outer packaging box of standard shape in polypropylene with a transparent film in polyolefines



The implant identification is performed by the presence of the product label on the external lid, visible from the window of the outer packaging box.

The detailed description of each elements composing this packaging is located in part III of the MET 02/001 report « Presentation of the various packaging components » *[see Annex CIII.1]* .We can find the following elements, per component :

↳ PIP technical documents
↳ material description and type
↳ suppliers
↳ sizes
↳ general and physicochemical properties
↳ microbial barrier properties
↳ product expiry date
↳ conclusion on the product choice