Agence nationale de sécurité du médicament et des produits de santé

Meeting minutes

Document date 17/06//2016

Division: Division for therapeutic medical devices and cosmetics

Unit: Consumer medical devices and cosmetics

Head of department: Brigitte Heuls

TEMPORARY SPECIALIST SCIENTIFIC COMMITTEE

"Breast implant biocompatibility evaluation strategy"

Meeting of 01/02/2016

Participants	Status	Present	Absent /excused
Brigitte Heuls	Director of the division for therapeutic medical devices and cosmetics (DMTCOS)	☒	
Thierry Thomas	Deputy Director-DMTCOS	☒	
Hélène Duvignac	Consumer medical devices and cosmetics team manager	☒	
Cécile Verdier	Expert toxicologist-DMTCOS	☒	
Joëlle Amédée (telephone)	Member	☒	
Pierre Cuq (video)	Member	☒	
Fabrice Ganachaud (telephone)	Member	☒	
Daniel Perdiz	Member	☒	
Muriel Vayssade	Member	☒	
Xavier Garric (video)	Occasional expert	☒	

Updates	Subjects discussed	Action	EU opinion required prior to publication YES/NO	PDI YES/NO
1.	**Introduction**	Adoption	N	N
2.	**Background-reminder**	Adoption	N	N
3.	**TSSC objectives**	Adoption	N	N
4.	**Reminder on applicable standards for demonstrating textured breast implant biocompatibility**	Adoption	N	N
5.	**Summary of manufacturer biocompatibility data**	Adoption	N	N
6.	**Work method and deliverable**	Discussion and Opinion	N	N
7.	**Conclusions – Round table**	Adoption	N	N

143/147 boulevard Anatole France - F-93285 Saint-Denis Cedex - Tel.: +33 (0)1 55 87 30 00 - **www.ansm.sante.fr**

Meeting procedure

1. Introduction

The agenda is approved by the experts.

2. Background-reminder

As a reminder, the 27 cases of ALCL related to breast implants were declared to the ANSM.

In its opinion, the INCA states there is a clearly established relationship between this disease and breast implants, and mentions the need to look into the potential relationship between implant macro-texturing and onset of BIA-ALCL.

Therefore a TSSC was set up to evaluate the pathophysiological mechanism of occurrence of cases of ALCL in women with breast implants. The TSSC met 3 times in 2015, and the findings by the experts were as follows:

- There is a more severe inflammatory reaction from the body with textured implants.
- There is a reaction which involves immunological mechanisms between the textured breast implant surface and the patient (antigen stimulation and specific cytokine involvement).
- A textured breast implant should be considered as a separate medical device from a smooth breast implant.
- The characteristics of the textures vary greatly from one manufacturer to another (pore size, diameter, texturing height, etc.).
- Texture implant biocompatibility needs to be demonstrated.

The TSSC concluded on the following:

- The potentially different immune reaction between smooth and textured breast implants needs to be looked at more closely.
- The biocompatibility of textured implants with European legislation should be clearly documented.
- Biocompatibility data available and provided by manufacturers of textured implants needs to be analysed.

Demonstration of the biocompatibility of textured breast implants has been investigated. In May 2015, manufacturers of breast implants on the French market were therefore asked to provide:

- Information on biocompatibility tests for all breast implant ranges manufactured by each company.
- The procedure used by the company to conclude on the biocompatibility of the various breast implants tested and the different textures.

The ANSM looked into this data.

3. TSSC objectives

The Temporary Specialist Scientific Committee on the strategy to evaluate the biocompatibility of breast implants is to issue an opinion on the procedures used to demonstrate breast implant biocompatibility and on the admissibility of the relevant procedures.

This TSSC is separate from the ALCL TSSC.

Especially, this TSSC is to analyse the arguments provided by the manufacturers justifying non-conduction of tests, as provided for by harmonised standard ISO 10993-1 and subsequent standards.

Discussion
One expert asks why the issue of breast implant biocompatibility was excluded from the ALCL TSSC scope.
An ANSM representative answers that this TSSC on breast implant biocompatibility covers regulatory aspects. It is specified that it is not just because a manufacturer carries out all of the tests provided for by standard ISO 10993-1 that ALCL can be prevented. They are two different issues.
The experts are reminded that following the ALCL TSSC, the ANSM conducted several studies which began in 2016:

- Study of the characterisation of textured breast implant surface,
- Study of the evaluation of the pathogenic role of inflammation and chronic T-cell stimulation by the breast implant shell (study on special mice in which shell fragments were implanted),
- Study of the bioclinical parameters observed in women with ALCL,
- Study of the genomic characterisation of ALCL (conducted by the INCA).

Finally, the possibility of integrating the results of this TSSC with those of that for ALCL if necessary is not ruled out.

One expert asks which data is currently available on texturing (physical and biological parameters etc.)
An ANSM representative answers that there is no consensus as to texturing parameters or as to the terms "microtextured, textured, macrotextured" between manufacturers. A study is ongoing to possibly establish a classification for the textures.

One expert asks if industrialists have been asked for feedback on the ALCL TSSC's conclusions and what their reaction might have been.
An ANSM representative answers that there was a meeting with all manufacturers marketing their breast implants in France in October 2015. The TSSC's conclusions were submitted to them along with anonymous data from initial findings on the biocompatibility data for each of the manufacturers. The information did not give rise to any specific questions from the manufacturers.

4. Reminder on applicable standards for demonstrating textured breast implant biocompatibility

The regulatory tools used by the ANSM to analyses the manufacturers' biocompatibility data are presented. It is specified that compliance with the harmonised standards cited below is synonym to conforming to the requirements of directive 93/42/EEC, however manufacturers can also use other methods to demonstrate biocompatibility, on the condition they show their relevance to and equivalence with the standard method.

- Point 7.1 of Directive 93/42/EEC: sets out the essential requirements on device compatibility with human tissue, with which the breast implants must comply.
- Harmonised standard ISO 10993-1: gives presumption of compliance with the essential requirements and indications for the biological evaluation of medical devices, stating the applicable biocompatibility tests.
- Harmonised standard ISO 14607 on breast implants: evaluating the potential short and long-term effects, including cytotoxicity, irritation, haemocompatibility, genotoxicity, implantation, immunotoxicity, other forms of systemic toxicity, reproductive toxicity and carcinogenicity. This standard also stipulates that the effects of the shell surface texture on surrounding tissue should be assessed
- Reminder on the Commission's message of 15.11.2001(1)

Manufacturers' can also meet regulatory requirements:

- Either by providing a strategy for demonstrating biocompatibility, with scientific reasoning
- By carrying out biocompatibility tests,
- Or by justifying, where applicable, why they did not carry out tests, with supporting scientific evidence, literature searches and if necessary, demonstration of equivalence with another MD, the biocompatibility of which has already been demonstrated.

Note (1) : This communication deals about breast implants requirements at the time they were classified as class IIb. This document introduces specific measures in order to improve patient follow-up, patient information, as well as provides new guidance for quality control and fundamental research areas.

5. Manufacturer biocompatibility data evaluation summary

The 9 manufacturers marketing breast implants in France were contacted.
The ANSM questioned them in May and October 2015:

- Information on biocompatibility tests for all breast implant ranges was requested,
- They were asked to provide the procedure used to conclude on the biocompatibility of the various breast implants tested and the various textures,
- They were asked to demonstrate the impact from texturing in terms of biocompatibility with certain biological characteristics.

The following were received from each manufacturer:

- A table of the biocompatibility tests carried out,
- Otherwise, arguments supporting biocompatibility.

Analysis of the manufacturers' data on texturing by the ANSM consisted of:

- Verifying if a response was brought for each biocompatibility characteristic provided for by legislation covering this type of MD,
- Providing results for the gel, shell and finished product,
- Presenting the summary taking account of demonstration of texturing biocompatibility [shell + finished product].

From the manufacturers' data, it can be seen that:

- Among the tests provided by standard ISO 10993-1 (claimed), not all are carried out,
- In some cases, reasons for the tests not being carried out are provided.

Discussion:

One expert asks if the reasons for not carrying out the tests provided for (often based on general scientific literature) are used with the manufacturers' own implants so as to avoid carrying out tests.
One expert asks if the tests submitted by the manufacturers mention a risk from texturing.

Another expert asks if there is an official line within the TSSC, what type of tests should be proposed? Towards which type of literature should one turn to properly evaluate the risk of texturing for implants?
If a manufacturer has conducted all the tests but accidents occur due to texturing, this may mean that the tests are not sufficient, even if they have all been performed. However, if the texturing test is not useful, there's no point doing all the other tests.

An ANSM representative says the question was raised during the ALCL TSSC. It was finally decided that the standard recommended a certain number of tests but was probably not sufficient, and that it would be useful to conduct other tests in order to understand texturing.

This is why the TSSC was asked to evaluate the question for a purely regulatory standpoint, in order to determine whether the manufacturers effectively meet the requirements of the legislation.
However, other types of tests will probably be necessary.

The expert adds that at the same time it will be necessary to issue recommendations to complete the standard.

The ANSM answers that it could be put to the ALCL TSSC. If a manufacturer has carried out all the tests, it will only apply to textured implants. It is not possible at this time to say whether the same texture is used from one manufacturer to another. This is why work on a classification has begun. Many questions remain on the subject.

6. Work method and deliverable

The question to which the ANSM must answer is the following: Is the biocompatibility of textured breast implants demonstrated?

In order to determine whether the arguments provided by the manufacturers to support the fact tests have not been carried out are scientifically acceptable, each of the rationales has been analysed and the arguments evaluated by biological effect. The objective is to provide an opinion as to whether the arguments cited by the manufacturers are relevant and substantiated, and this by biological effect. The working methodology was therefore divided into 3 steps, as shown below:

WORKING METHODOLOGY PROPOSAL		DELIVERABLES
Step 1	Main arguments versus biological effects or opposite	**DELIVERABLE 1:** **TSSC's opinion of 15/03/16** on the admissibility of each argument (vote)
Step 2	Combination of arguments per biological effect	**DELIVERABLE 2:** TSSC's opinion of 15/03/16 on the combination of arguments per biological effect (vote)
Step 3	Recommendation on the strategy to be implemented to demonstrate textured breast implant biocompatibility	**DELIVERABLE 3:** Official line

Step 1 consists of issuing an opinion as to whether the main arguments per individual biological effect are relevant and substantiated. Then, for each biological effect, several arguments can be claimed by the manufacturer, and these will be known as combinations of arguments. This is step 2 for which an opinion is to be issued on whether the combinations of arguments are relevant and substantiated. Finally, in a third step, the TSSC is asked to determine a strategy for demonstrating the biocompatibility of textured breast implants in order to take an official line.

Discussion:

One expert says that the number of cases of ALCL could have been provided with regards to the manufacturers' arguments.
An ANSM representative recalls that the main objective of the TSSC is to determine whether the methodology used by manufacturers is acceptable or not for demonstrating biocompatibility.

The tables of the individual arguments by biological effect are then presented to the experts and they are asked to vote on each argument.
The results of the votes are given in the tables below. There are 5 expert's votes for each argument.

Biological effects	Number of arguments taken separately	RESULT OF THE VOTES ON ALL ARGUMENTS BY BIOLOGICAL EFFECT a) Relevant argument b) Substantiated argument N: No A: Abstention Y: Yes
General biocompatibility	6	a) 23N, 6A, 1Y b) 27N, 3A
Carcinogenicity	8	a) 35N, 3A, 2Y b) 40N
Immunotoxicity	7	a) 16N, 11A, 8Y b) 24N, 8A, 3Y
Reproductive and developmental toxicity	2	a) 8N, 2A b) 8N, 2A
Teratogenicity	1	a) 5N b) 5N
Toxicokinetics	7	a) 27N, 7A, 1Y b) 28N, 7A
Biodegradation	7	a) 34N, 1A b) 34N, 1A
Implantation	1	a) 5N b) 5N
Acute systemic toxicity	1	a) 5N b) 5N
Specific organ toxicity	1	a) 5N b) 5N

7. Conclusion

The individual arguments put forward by the manufacturers were evaluated by the experts on the TSSC. Most arguments, taken separately, are neither relevant nor substantiated to be able to justify not carrying out biocompatibility tests on textured breast implants.
The next TSSC meeting will cover the continuing work on votes on the combinations of arguments put forward by the manufacturers especially.

Next Breast Implant Biocompatibility TSSC meeting: 15 March 2016