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USP <87> AND USP <88> TEST SUMMARY REPORT OF FLON-CHEM 1050 BLUE

Quotation:
VZB2PH210202-02

Sponsor:
FF.GI. srl
Via della Molinara 77/79
24064 Grumello del Monte
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1 General information

Item Generic Name:	FLON-CHEM 1050 BLUE
Item Trade Name:	FLON-CHEM 1050 BLUE
Sponsor's Name and Address:	FF.GI. srl Via della Molinara 77/79 24064 Grumello del Monte Italia

2 Item description

As reported by the Sponsor, "FLON-CHEM 1050 BLUE" is a raw material consisting of blue plastic disc.

3 USP Pharmacopoeia

United States Pharmacopoeia (USP) chapter <1031> provides guidance on the identification and performance of procedures for evaluating the biocompatibility of drug containers, elastomeric closures, medical devices, and implants [1]. Biocompatibility refers to the tendency of these products to remain biologically inert throughout the duration of their contact with the body. The biocompatibility testing procedures referenced in this chapter are designed to detect the nonspecific, biologically reactive, physical or chemical characteristics of medical products or the materials used in their construction. In combination with chemical assays, these biological procedures can be used to detect and identify the inherent or acquired toxicity of medical products prior to or during their manufacturing and processing.

To facilitate the identification of appropriate testing procedures, medical devices are divided and subdivided, as shown in Table 1, according to the nature and extent of their contact with the body. Major categories of medical devices are surface devices, external communicating devices, and implant devices. These are then further subcategorized. Some examples of medical devices and implants belonging to each of the subcategories are also presented in Table 1.

Device Category	Device Subcategory	Nature or Extent of Contact	Some Examples
Surface Devices	Skin	Devices that contact intact skin surfaces only	Electrodes, external prostheses, fixation tapes, compression bandages, and monitors of various types
	Mucosal Membrane	Devices communicating with intact mucosal membranes	Contact lenses, urinary catheters, intravaginal and intraintestinal devices (stomach tubes, sigmoidoscopes, colonoscopes, gastroscopes), endotracheal tubes, bronchoscopes, dental prostheses, orthodontic devices, and intrauterine devices
	Breached or Compromised Surfaces	Devices that contact breached or otherwise compromised body surfaces	Ulcer, burn, and granulation tissue dressings or healing devices and occlusive patches
External Communicating Devices	Blood Path, Indirect	Devices that contact the blood path at one point and serve as a conduit for entry into the vascular system	Solution administration sets, extension sets, transfer sets, and blood administration sets
	Tissue, Bone, or Dentin Communicating	Devices and materials communicating with tissue, bone, or pulp and dentin system	Laparoscopes, arthroscopes, draining systems, dental cements, dental filling materials, and skin staples
	Circulating blood	Devices that contact circulating blood	Intravascular catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, dialyzers, dialysis tubing and accessories, hemoadsorbents, and immunoadsorbents
Implant Devices	Tissue or Bone	Devices principally contacting bone or principally contacting tissue and tissue fluid	Examples of the former are orthopedic pins, plates, replacement joints, bone prostheses, cements, and intraosseous devices; examples of the latter are pacemakers, drug supply devices, neuromuscular sensors and simulators, replacement tendons, breast implants, artificial larynxes, subperiosteal implants, and ligation clips
	Blood	Devices principally contacting blood	Pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts, internal drug delivery catheters, and ventricular-assist devices

Table 1: Classification and Examples of Medical Devices [1].

Each category of devices is subcategorized and then even further subdivided according to the duration of the contact between the device and the body. The duration of contact is defined as (A) limited (less than 24 hours); (B) prolonged (24 hours to 30 days); or (C) permanent (more than 30 days).

To provide guidance on selecting the appropriate plastic or other polymer class designation for a medical device, each subcategory of Surface Devices (see Figure 1) and External Communicating Devices (see Figure 2) is assigned a USP Plastic Class designation [1].

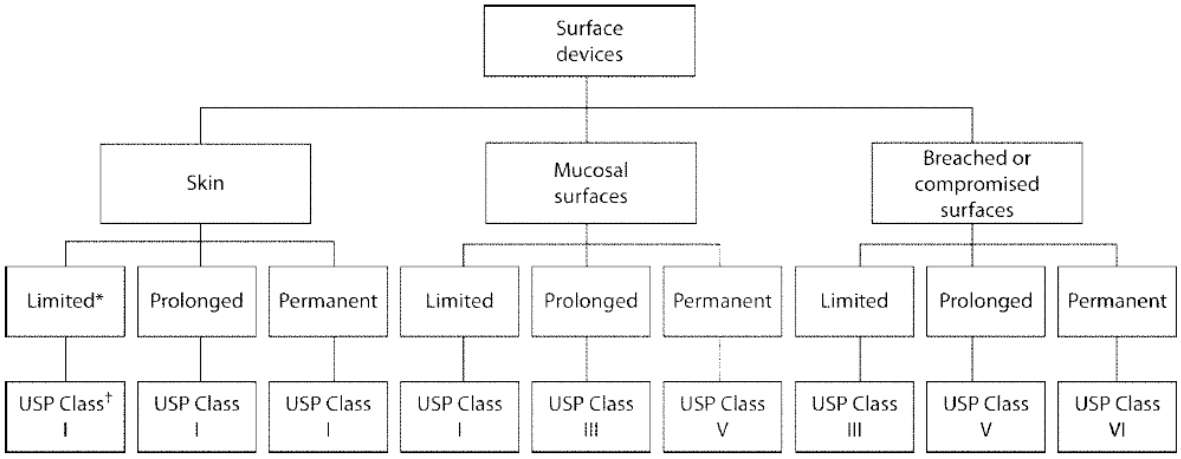

Figure 1: USP plastic and other polymer class requirements for surface devices [1].

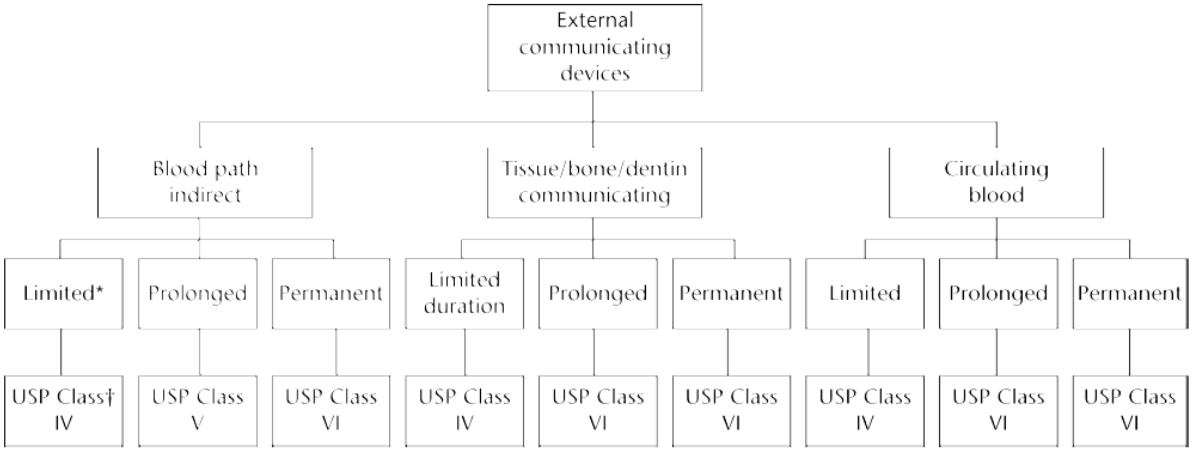

Figure 2: USP plastic and other polymer class requirements for external communicating devices [1].

The indicated numerical class number increases relative to the duration (risk) of contact between the device and the body. In the category of Implant Devices, the exclusive use of class VI is mandatory.

The assignment of a plastic or other polymer class designation to a subcategory is not intended to restrict the use of higher classes of plastics or other polymers. Although the assigned class defines the lowest numerical class of plastic or other polymer that may be used in the corresponding device, the use of a numerically higher class of plastic is optional. When a device can be defined as belonging to more than one device category, the plastic or other polymer should meet the requirements of the highest numerical class.

The biocompatibility of the plastic, other polymeric, and elastomeric portions of these products are tested according to the procedures described under Biological Reactivity Tests, In Vitro <87> [2]. If a class designation for a plastic or other polymer is also required, three appropriate testing procedures described under Biological Reactivity Tests, In Vivo <88>. are performed [3].

These three tests are applied to materials or medical devices, if there is a need for classification of plastics and other polymers based on *in vivo* biological reactivity testing.

Six Plastic Classes are defined (see Table 2). This classification is based on responses to a series of in vivo tests for which extracts, materials, and routes of administration are specified. These tests are directly related to the intended end-use of the plastic articles. The choice of extractants is representative of the vehicles in preparations with which the plastics are likely to be in contact.

Plastic Classes[a]						Tests to be Conducted			
I	II	III	IV	V	VI	Test Material	Animal	Dose	Procedure[b]
x	x	x	x	x	x	Extract of *Sample* in *Sodium Chloride Injection*	Mouse	50 mL/kg	A (IV)
							Rabbit or Guinea Pig	0.2 mL/animal at each of 10 or 6 sites	B (IC)
	x	x	x	x	x	Extract of *Sample* in *1 in 20 Solution of Alcohol in Sodium Chloride Injection*	Mouse	50 mL/kg	A (IP)
							Rabbit or Guinea Pig	0.2 mL/animal at each of 10 or 6 sites	B (IC)
		x		x	x	Extract of *Sample* in *Polyethylene Glycol 400*	Mouse	10 g/kg	A (IP)
							Rabbit or Guinea Pig	0.2 mL/animal at each of 10 or 6 sites	B (IC)
		x	x	x	x	Extract of *Sample* in *Vegetable Oil*	Mouse	50 mL/kg	A (IP)
							Rabbit or Guinea Pig	0.2 mL/animal at each of 10 or 6 sites	B (IC)
			x		x	Implant strips of *Sample*	Rabbit	4 strips/animal	C
			x		x	Implant *Sample*	Rat	2 *Samples*/animal	C

Table 2: Classification of Plastics. Tests required for each class are indicated by "x" in appropriate columns. Legend: A (IP)—Systemic Injection Test (intraperitoneal); B (IC)—Intracutaneous Test (intracutaneous); C—Implantation Test (intramuscular or subcutaneous implantation).

The Systemic Injection Test and the Intracutaneous Test are designed to determine the systemic and local, respectively, biological responses of animals to plastics and other polymers by the single-dose injection of specific extracts prepared from a Sample.

The Implantation Test is designed to evaluate the reaction of living tissue to the plastic and other polymers by the implantation of the sample itself into animal tissue.

With the exception of the Implantation Test, the procedures are based on the use of extracts that, depending on the heat resistance of the material, are prepared at one of three standard temperatures: 50°, 70°, and 121°. Therefore, the class designation of a plastic must be accompanied by an indication of the temperature of extraction.

Plastics may be classified as USP Plastic Classes I–VI only on the basis of the response criteria prescribed in Table 2. This classification does not apply to plastics that are intended for use as containers for oral or topical products, or that may be used as an integral part of a drug formulation, and it does not apply to natural elastomers, which are to be tested in Sodium Chloride Injection and vegetable oils only. These tests are designed for application to plastics and other polymers in the condition in which they are used. If the material is to be exposed to any cleansing or sterilization process prior to its end-use, then the tests are to be conducted on a Sample prepared from a specimen preconditioned by the same processing.

4 Summary of *in vitro* biological reactivity tests

The test item “FLON-CHEM 1050 BLUE” in the test, representative of the evaluated plastic, has been tested for cytotoxicity by elution test following USP <87> [2] at Test Facility Eurofins Biolab S.r.l..

The study was carried out in order to evaluate any biological reactivity of mammalian cell cultures following contact with the test item extract. A subconfluent NCTC clone 929 cell culture in exponential phase of growth was used.
An extract of the test sample was prepared considering a surface/volume ratio of 3 cm^2/ml in supplemented culture medium at 37±1°C in a 5±1% CO_2 atmosphere for 24 hours in static conditions.

The extract was used for the test. The assay sample (extract of test item) was applied to the monolayer and was incubated at 37±1°C in 5±1% CO_2 atmosphere for 48 hours.

After incubation the cells were observed under the light microscope to evaluate the biological reactions.

After 24 and 48 hours of contact in the wells treated with the test sample extract some discrete intracytoplasmic granules were present, no cell lysis was observed (reactivity grade 0).

As reported in Eurofins Final Report LV21AA8860-1 dated July 6th 2021, the test item **MEETS** the requirements of the test.

Test results are summarized below in Table 3.

Test performed	Standard method	Test report number	Conclusion
Cytotoxicity by elution test	USP <87> [2]	Analytical Report: AAP44558 Eurofins Sample Number: LV21AA8860-1 Version: 1 Dated July 6th 2021	Requirements satisfied

Table 3: Summary of *in vitro* biological reactivity tests.

5 Summary of *in vivo* biological reactivity tests

The test item called “FLON-CHEM 1050 BLUE” in the test, representative of the evaluated plastic, has been tested for systemic injection, intracutaneous reactivity and implantation test following USP <88> [3] at Test Facility Eurofins Biolab S.r.l..

The study was carried out in order to grade the test material as USP class VI-50°C.

5.1 Systemic injection test

This test is designed to evaluate systemic responses to the extracts of materials under test following injection into mice. Four extracts of the test sample were prepared using as extracting liquids: Sodium Chloride Injection, Cottonseed oil, PEG 400 and Ethylic Alcohol + Sodium Chloride Injection (1:20).

In the systemic toxicity test, sample extracts were intravenously or intraperitoneally injected in four group of 5 mice. Other four groups were used for the relative control solvents. Each symptomatology discovered within 72 hours of observation was recorded.

No toxic symptoms were observed immediately after the administration and 4, 24, 48 and 72 hours after the treatment.

As reported in Eurofins Final Report STULV21AA3862-1 dated August 31st 2021, the test item **MEETS** the requirement for systemic injection test.

5.2 Intracutaneous test

This test is designed to evaluate local responses to the extracts of materials under test following intracutaneous injection into rabbits. Four extracts of the test sample were prepared using as extracting liquids: Sodium Chloride Injection, Cottonseed oil, PEG 400 and Ethylic Alcohol + Sodium Chloride Injection (1:20).

The evaluation of intracutaneous reactivity has been performed by intracutaneously injecting each extract in five sites of 2 albino rabbits. Solvents were administrated with the same procedure and was used as control.

24, 48 and 72 hours after the treatment, all sites treated with Sodium Chloride Injection extract, PEG 400 extract, Ethylic Alcohol + Sodium Chloride Injection (1:20) extract and all control sites treated with Sodium Chloride injection, PEG 400, Ethylic Alcohol + Sodium Chloride Injection (1:20) showed no sign of erythema nor sign of oedema.

24, 48 and 72 hours after the treatment, all sites treated with Cottonseed oil extract and all control sites treated with Cottonseed Oil showed a slight erythema and no sign of oedema.

As reported in Eurofins Final Report STULV21AA3862-1 dated August 31st 2021, the test item **MEETS** the requirement for intracutaneous test.

5.3 Implantation test

The implantation test is designed for the evaluation of plastic materials and other polymeric materials in direct contact with living tissue. Of importance are the proper preparation of the implant strips (or discs) and their proper implantation under aseptic conditions.

To perform the implantation test, the test sample was inserted in two sites underneath the skin: one disc in the right caudal region and one disc in the right cranial region of the dorsal surface, laterally of the rachis of each of five rats. In a similar way two discs of USP High-Density Polyethylene were implanted underneath the skin, laterally on the opposite side (left cranial region and left caudal region) of the rachis of each animal.

The rats were sacrificed 7 days after the treatment and all sites of implantation were observed macroscopically to evaluate the eventual encapsulation.

In all the treated and control sites, no encapsulation has been observed.

As reported in Eurofins Final Report STULV21AA3862-1 dated August 31st 2021, the test item **MEETS** the requirement for implantation test.

6 Conclusions drawn from *in vivo* biological reactivity tests

Test results from *in vivo* biological reactivity tests are summarized below in Table 4.

Test performed	Standard method	Test report number	Conclusion
Systemic injection test	USP <88> [3]	Analytical Report: AAQ53666, Eurofins Number: STULV21AA3862-1, Version: 1 dated August 31st 2021	Requirements satisfied
Intracutaneous test	USP <88> [3]		Requirements satisfied
Implantation test	USP <88> [3]		Requirements satisfied

Table 4: Summary of *in vivo* biological reactivity tests

Based on results obtained from tests done according to USP <88> current edition [3], the tested item "FLON-CHEM 1050 BLUE", representative of the evaluated plastic, satisfies **USP class VI-50°C** requirements and it can be used as plastic material for all medical devices categories described in USP [1].

7 Filing

All data and recordings related to this evaluation are filed in the archives of Eurofins Biolab S.r.L for ten years after the issuing of the final report.

At the end of the conservation period, the Sponsor may request an extension of the conservation of all or part of the products for a further period, or their restitution. A suitable agreement shall be drafted in this case.

8 Procedures

All procedures used during this evaluation are recorded in the Test Facility Eurofins Biolab S.r.l.

9 Normative references and bibliography

[1] "United States Pharmacopeia (USP) and the National Formulary (NF) USP 43–NF 38 <1031> THE BIOCOMPATIBILITY OF MATERIALS USED IN DRUG CONTAINERS, MEDICAL DEVICES, AND IMPLANTS." .

[2] "United States Pharmacopeia (USP) and the National Formulary (NF) USP 43–NF 38 <87> BIOLOGICAL REACTIVITY TEST, IN VITRO." .

[3] "United States Pharmacopeia (USP) and the National Formulary (NF) USP 43–NF 38 <88> Biological Reactivity Tests, In Vivo." .

10 Signatures

Persons listed below confirm the contents of the present Plastic Classification Document regarding “FLON-CHEM 1050 BLUE” with their signatures.

Electronic signatures are at the bottom of this page.

The present document is managed using the internal software eLIMS-BPT.

eLIMS-BPT employs electronic signature to signify approval of final reports. The electronically signed records include controls to confirm the authenticity of the signature on signed documents. Audit trails are captured to identify signing events and changes to electronic signature records. eLIMS-BPT is designed and validated to conform to requirements of 21 CFR Part 11.

Any extrapolation to other devices is the Sponsor’s responsibility.

The statement was prepared based upon the information provided by the Sponsor, the author is not responsible for the correctness of this supplied information.

The author does not assume any liability for potential biological hazards or adverse clinical reactions that may be caused by the materials and/or medical devices used.

Biological investigations shall be followed by careful observations for unexpected adverse reactions or events in humans during use of the final medical device, part or accessory.

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