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SHARING EXPERTISE

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HISTOACRYL, HISTOACRYL® LAPFIX and HISTOACRYL PROSET OFX- FSCA
Health Hazard Evaluation

To whom it may concern:

Rubí, 07.04.2021

RISK ASSESSMENT☒	
Origin of the new risk:	1. Complaints [redacted] and [redacted] received from customers claiming that the glue was lacking its adhesive properties. 2. Batches in the warehouse manufactured from the same Raw Material batch that one of those which were claimed in [redacted] (Lot Nº 220445N2) were found to share the same deviation. 3. Since September 2020, 6 customer complaints related to the lack of adhesive properties of Histoacryl® have been received
Hazard:	Function
Foreseeable sequence of events:	Performance features of the product do not meet the demands of the application/implantation, in this sense, device is not achieving the Intended Use. Root cause analysis, aimed at elucidating the sequence of events that led to the deviation, is in progress.
Hazard situation:	Nonfunctional product: SKIN CLOSURE: Wound edges are not properly approximated. MESH FIXATION: Hernia mesh cannot be fixed. SCLEROTHERAPY: Slight delay in polymerization.
Harm:	SKIN CLOSURE: Wound dehiscence or insufficient closure, bleedings. Risk of infection, pain, bad cosmetic result, irritation, inflammation. Need of medical treatment or reoperation. Operating time extension.

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	MESH FIXATION: Risk of alternative mesh fixation technique. Operating time extension. SCLEROTHERAPY: Risk of alternative medical intervention. Operating time extension.
Probability of occurrence before corrective actions/ activities:	Remote (**) (*) Estimated/ (**) Calculated (14 complaint received for Histoacryl does not stick in more than 7.000.000 units sold between 01.2016-01.2021)
Corrective Actions/ Activities:	Root Cause Analysis and Corrective Actions are to be defined in the framework.
Probability of occurrence after corrective actions/ activities:	Improbable
Severity:	Serious
RISK ACCEPTED	YES

ACCEPTANCE:

Histoacryl® is a sterile, liquid tissue adhesive consisting of n-butyl-2-cyanoacrylate (NBCA).

Histoacryl® is indicated for:

- SKIN CLOSURE: Closure of skin wounds without tension (from clean surgical incisions, including clean surgical incisions and incisions from minimally invasive surgery), and simple, thoroughly cleansed, trauma-induced lacerations.
- SCLEROTHERAPY: Sclerotherapy of large oesophageal or fundal varices.
- MESH FIXATION: Fixation of hernia meshes, especially in inguinal hernia surgery.

The primary material used to construct Histoacryl® tissue adhesive is n-butyl-2-cyanocrylate (NBCA).

The NBCA raw material used to produce Histoacryl® product family is supplied by Cyberbond Europe GmbH (NBCA Cyberbond 7010, Material Code 21090090) as liquid monomer with a minimum purity of 98%A.

Adhesive Strength has been identified as relevant performance characteristic of the product. Considering this parameter, Finished Product Specification (FPS) of Histoacryl® and Histoacryl® L were defined *(FPS/02/HSV & FPS/02/HSL).*

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Investigation

A. Evaluation of available samples from complaints:

Received samples were analyzed in terms of Adhesive Force, critical performance characteristic of the product related to its adhesiveness properties. Obtained results are listed below:

1. Complaint [redacted]:
   - REF [redacted] Batch 220171N1 (Complained batch) – 1 out of 2 ampoules samples received showed a curing behavior slower than expected and the polymerization was not complete in testing conditions of adhesive force test. However, both tested samples fulfilled specification for Adhesive Force collected in the FPS but showing lower adhesive force than usual.
   - REF [redacted] - Batch 220112N1 – the adhesive inside the ampoule showed a curing behavior slower than expected and the polymerization was not complete in testing conditions of adhesive force test. However, tested samples fulfilled specification for Adhesive Force collected in the FPS but showing lower adhesive force than usual.
   - REF [redacted] - Batch 220143N1 - the only sample received showed a curing behavior slower than expected and the polymerization was not complete in testing conditions of adhesive force test. However, tested sample fulfilled specification for Adhesive Force collected in the FPS but showing lower adhesive force than usual.
   - REF [redacted] - Batch 219442N2 – the only sample received showed an acceptable performance in terms of Adhesive Force test results and curing behavior.

2. Complaint [redacted]: No samples received but a video showing the non-sticky behavior.
   - REF [redacted] - Batch 220364N2

3. Complaint [redacted]: 3 unopened pouches received.
   - REF [redacted] - Batch 220445N2 – the three samples received showed a curing behavior slower than expected and the polymerization was not complete in testing conditions of adhesive force test. However, tested samples fulfilled specification for Adhesive Force collected in the FPS but showing lower adhesive force than usual.

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B. Evaluation of samples available in stock related to complaints

Batches in the warehouse manufactured from the same Raw Material batch that Lot Nº 220445N2 (complaint [redacted]) were found to share the same deviation. Specifically, when REF [redacted] - Lots Nº 220451N2 & 220451N3 were analyzed in terms of Adhesive Force. It was concluded that some representative samples gave lower adhesive forces in average, even few of them failed the adhesive strength test giving results below 20 N, below the specification.

Reference - Batch	Result
[redacted] - 220451N2	Not fulfil specification
[redacted] - 220451N3	Not fulfil specification

C. Evaluation of samples available in stock

Other batches available in the warehouse were also analyzed in terms of Adhesive Force. It was concluded, for all batches tested listed below, that the adhesive formulation did not completely polymerize at testing conditions, showing an unexpected curing behavior.

Reference - Batch	Result
[redacted] - 220404N2	Not fulfil specification
[redacted] - 220405N2	Not fulfil specification
[redacted] - 220474N1	Not fulfil specification
[redacted] - 221024N1	Not fulfil specification
[redacted] - 221012N1	Not fulfil specification

Summary of code-batches of which we have evidence that the product did not completely polymerize:

Reference	Batch	Indication
[redacted]	220404N2	Wound closure, sclerotherapy & mesh fixation
	220405N2	Wound closure, sclerotherapy & mesh fixation
	220474N1	Wound closure, sclerotherapy & mesh fixation
	221012N1	Wound closure, sclerotherapy & mesh fixation
	220451N2	Wound closure, sclerotherapy & mesh fixation
	220451N3	Wound closure, sclerotherapy & mesh fixation

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Reference	Batch	Indication
[redacted]	221024N1	Wound closure, sclerotherapy & mesh fixation
	220171N1	Wound closure, sclerotherapy & mesh fixation
	220112N1	Wound closure, sold only in CN and this reference is only approved for this indication
	220143N1	Wound closure, sclerotherapy & mesh fixation
	220364N2	Wound closure, sclerotherapy & mesh fixation
	220445N2	Wound closure, sclerotherapy & mesh fixation

D. Root Cause Investigation

The investigation of the root cause is still on-going. The current state of the investigation suggests that the most likely cause of the deviation is that the concentration of protons in the raw material monomer solution, and consequently in the corresponding finished goods, is higher than expected, resulting in the observed polymerization delay. Such an effect is reported in the literature as cyanoacrylate polymerization is very sensitive to slightly acidic environments. The unusual delayed polymerization profile is clearly observed in the induction and polymerization time obtained by Differential Scanning Calorimetry (DSC) in specific testing conditions being possible to correlate the behavior of raw material and finished goods. Such delay is assessed in the corresponding risk assessment section.

On the other hand, lower adhesive strength forces can be to the same root cause, as acidity can modify the expected polymerization profile and consequently the bonding to the of surfaces in contact. Such risk required further testing described in the next section.

E. Further Analysis

Adhesive Force test performed according to internal standard comprises curing 1 drop of NBCA based adhesive in between metal strips that are thoroughly cleaned with acetone & dried prior to testing. When deposited between the metal plates, NBCA cures through the anionic polymerization pathway activated by the traces of moisture that might be present on the surface of the metal plates after cleaning & drying, as well as due to the very slight penetration of ambient moisture.

Adhesive Force test was established as a standardized method for quality control in the manufacturing of Histoacryl® product family, thus not being intended to mimic the conditions of clinical use of the product.

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Alkyl cyanoacrylate monomers structure consists of a double carbon ethylene group with two reactive electro-withdrawing functions: cyano (-CN) and ester (-COOR), that exhibit a remarkable reactivity towards nucleophiles, thus explaining their rapid polymerization rate. Even water and traces of weak bases are sufficient to initiate the polymerization. Mode of Action of Histoacryl® is based on the rapid polymerization of the alkyl cyanoacrylate family when in contact with ionic solutions, such as tissue fluids, blood plasma and saline solutions. Specifically, when used as vascular embolization agent, such in sclerotherapy of varices, Histoacryl® undergoes rapid polymerization catalyzed by nucleophiles found in blood or on the vascular endothelium.

Considering all the above, polymerization of Histoacryl® at conditions of Adhesive Force test is judged to represented a worst case testing environment when compared to the conditions of clinical use of the product. Accordingly, further analysis have been performed to evaluate the polymerization behavior of finished product batches related to observed delay in polymerization using in-vitro pre-clinical tests to characterize the potential clinical impact of such delay.

STUDIES RELATED TO SCLEROTHERAPY

The polymerization of Histoacryl® and Histoacryl mixtures with Lipiodol® 1:1 were evaluated when in contact with blood. It was concluded that Histoacryl® batches affected by the deviation instantly polymerized in contact with blood, and no delay could be appreciated. Evaluation of Histoacryl®/Lipiodol® 1:1 mixtures pointed to a slight difference (few seconds only) in polymerization when compared to samples not affected by the deviation.

Note: when used as vascular embolization agent, Histoacryl® is usually combined with an oily contrast medium (Lipiodol®), that allows polymerization time adjustment as well as fluoroscopic monitoring of delivery of the adhesive (NBCA is radiolucent, i.e. not radiopaque).

Those results have been evaluated by physician experts using the associated surgical techniques included in the indications of the product. The conclusion is that the clinical risk for patients, even in the worst cases, is acceptable as the product behaves as expected without significant clinical impact, given that the likelihood of harm occurrence is deemed extremely improbable and the severity of such defect is considered as non-critical.

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STUDIES RELATED TO MESH FIXATION

An in-vitro study was performed aiming to assess the breaking load of the fixation of a hernia mesh to a biological substrate using Histoacryl®. The breaking load is related to the strength necessary to fully detach the mesh by tensile force applied perpendicular to the biological substrate surface.

Two batches of Histoacryl® showing unexpected curing behavior at Adhesive Force testing conditions (REF [redacted] LOTS 220451N2 & 220405N2) were analyzed and compared to samples not affected by the deviation.

It was concluded that even delayed polymerization samples were able to polymerize at testing conditions. Nevertheless, affected batches showed lower breaking load values than non affected batches: X_{ave} = 8.7 N (LOT 220405N2) & 10.3 N (LOT 220451N2) vs. X_{ave} = 20.9 N & 25.0 N.

STUDIES RELATED TO SKIN CLOSURE

Two batches of Histoacryl® showing unexpected curing behavior at Adhesive Force testing conditions (REF [redacted] LOTS 220451N2 & 220404N2) were analyzed in terms of Wound Closure Strength (*).

Based on the requirements of the standard ASTM F2458-05, Wound Closure Strength method is intended "for comparison of tissue adhesives used to help secure the apposition of soft tissue". As stated in the standard, it is noted that a correlation of the results of the test method with actual adhesive performance in live human tissue has not been established.

(*) ASTM F2458-05 – Standard Test Method for Wound Closure Strength of Tissue Adhesives and Sealants as recommended in Guidance for Industry and FDA Staff Class II Special Controls Guidance Document: Tissue Adhesive with Adjunct Wound Closure Device Intended for the Topical Approximation of Skin.

Test results of Batches 220451N2 & 220404N2 were compared to available Wound Closure Strength test results of different lots of finished product of Histoacryl® produced from 2016 onwards.

It was stated that there was not enough evidence to conclude that batches showing an unexpected curing behavior at Adhesive Force testing conditions showed unacceptable results in the Wound Closure Strength test.

Risk assessment

Histoacryl® can be used for wound closure, mesh fixation or sclerotherapy in gastric varices according to the approved indications.

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In the particular case of **skin closure**, Histoacryl® is intended to be used topically, in Hospitals or outpatient areas. If a delay in the polymerization occurs or even if the product is not functional it could be easily detectable by the sanitary staff. A delay in the polymerization in this indication is not directly linked to harm to the patient, in most of the cases re-intervention or an extra medical treatment could probably not be necessary mainly because according to the IFU, Histoacryl® must be used in conjunction with and not in substitution of subcuticular sutures.

In case that the defective units were not detected, could cause wound dehiscence, local infections, pain, irritation, inflammation, impaired aesthetic outcome, operating time extension and could need medical treatment or re-intervention using another closure device.

As per our experience and knowledge, defective devices in that indication would be discarded and no serious harms would be expected to the patient, only a delay in the intervention if it is the case.

In the case of **mesh fixation**, the adhesive force is mainly needed to avoid the mesh displacement during the surgical intervention because after the abdominal wall closure the mesh will remain in a natural manner fixed by the surrounding layers, no higher loads are supported by the adhesive and, in consequence, no risks for patients except an operating time extension if the medical staff decide to apply an alternative fixation technique.

In the particular case of **sclerotherapy use**, after a deep analysis of the samples it can be concluded that the behavior of the adhesive is according to the requirements and only a slight delay in the polymerization can be seen, therefore the potential harm could led to a manageable situation only causing operating time extension due a potential requirement of an alternative medical intervention.

Therefore, according to the obtained results, the residual risk of Histoacryl® not being functional is ACCEPTED for all indications.

[redacted]

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