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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, 19.04.2021

RISK ASSESSMENT☒	
Origin of the new risk:	1. Since September 2020, 7 customer complaints related to the lack of adhesive properties or polymerization delayed of Histoacryl® have been received. (See table 1). 2. Some batches in stock in B. Braun Surgical's warehouse were found to share the same deviation.
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, see points D and E.
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. MESH FIXATION: Risk of alternative mesh fixation technique. Operating time extension. SCLEROTHERAPY: Risk of alternative medical intervention. Operating time extension.

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Probability of occurrence before corrective actions/ activities:	Remote (Calculated: 15 complaints received for Histoacryl does not stick in more than 7.120.000 units sold between 01.2016-03.2021)
Corrective Actions/ Activities:	Extensive testing on Finished Product batches to check their conformity, and conformity of raw material batches of NBCA monomer (Material Code 21090090). Detail of Corrective Actions are to be defined in the framework of CAPA AK 201941155. See also point F.
Probability of occurrence after corrective actions/ activities:	Improbable
Severity:	Serious
RISK ACCEPTED	YES

ACCEPTANCE Contents:

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Introduction

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).*

Investigation

Complaints related (Table 1)

All complaints regarding "glue does not stick" or similar, including Polymerization time too long of products within the expiry date of the product have been collected.

CC Notification	Creation date	Reference	Product	Batch	Country	Results	Samples received?
400485282	09/09/2020	[redacted]	HISTOACRYL BLUE 0.5ML	220133N2	PT	Not Confirmed	Samples tested fulfilled specifications
400490373	21/10/2020		HISTOACRYL® LAPFIX X1	220093N1	ES	Not Confirmed	No samples received
400490374	21/10/2020		HISTOACRYL® LAPFIX X1	220093N1 & 220071N2	ES	Not Confirmed	No samples received

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400497261	16/12/2020	[redacted]	HISTOACRYL® LAPFIX X1	220171N1	ES	Confirmed	Yes, but all the Histoacryl Lapfix products from the center have been collected: Histoacryl 1050044 & batches received: 220171N1, 220112N1, 220143N1, 219442N2.
400498033	23/12/2020	[redacted]	HISTOACRYL BLUE TISSUE ADHESIVE 0.5ML	220364N2	ES	Confirmed	No samples received but video.
400500621	20/01/2021	[redacted]	HISTOACRYL BLUE TISSUE ADHESIVE 0.5ML	220445N2	GB	Confirmed	Yes
400510142	12/04/2021	[redacted]	HISTOACRYL BLUE 0.5ML	2200 84N2	CN	Not confirmed	No samples received

A. <u>Evaluation of available samples from complaints:</u>

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]: 5 unopened pouches received:

   REF [redacted] - Batch 220133N2– the 5 samples received showed an acceptable performance in terms of Adhesive Force test results.

2&3. Complaints [redacted]: No samples received. No evidence of product failure.

4. Complaint [redacted]:

   - REF [redacted] - Batch 220171N1 (Complained batch) – 1 out of 2 ampoules 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.

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- 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.

5. Complaint [redacted]: No samples received but a video showing the non-sticky behavior.
   - REF [redacted] - Batch 220364N2
6. 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.
7. Complaint [redacted]: No samples received. No evidence of product failure.

B. <u>Evaluation of samples available in stock related to complaints</u>

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

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C. Evaluation of samples available in stock

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

D. Further Analysis

Adhesive Force test performed according to internal standard comprises curing one 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.

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 represent 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 preclinical tests to characterize the potential clinical impact of such delay.

E. Root cause conclusion

After a revision of the supply and manufacturing process and an extensive testing of finished goods, related raw materials and freshly prepared Histoacryl formulation in order to understand the unusual behavior of the polymerization, the root cause investigation concluded that the proton concentration in some raw material

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monomer solutions were slightly higher than expected. Consequently, such slightly acidity resulted in the observed polymerization delay described in the complained finished goods.

Such an effect is already reported in the literature as cyanoacrylate monomer polymerization is very sensitive to acidic environments. The unusual delayed polymerization profile is clearly observed in the induction time and polymerization time determined by Differential Scanning Calorimetry, in specific testing, being possible to correlate those parameters with the observed delayed polymerization behavior in the affected batches.
Moreover, the investigation concluded that the origin of such slightly higher proton concentration was caused by sulfur dioxide gas (SO_2), a declared preservative in Histoacryl formulation (30-70 ppm) in order to avoid a premature polymerization of the glue. We note that SO_2 is in equilibrium with H+ and HSO_3 dissolved in the monomer solution, particularly in the water contained in the monomer solution (also in the range of ppm).

Therefore, the combination of SO_2 in the higher range of the specification, a low water content of the monomer solution and a careful handling by the supplier and B. Braun to avoid leakage of SO_2 during transport and storage led to a higher SO_2 dissolved in the monomer solution, resulting in more protons available in the solution, that finally modified the usual fast polymerization causing a delay. Therefore, SO_2 dissolved in the solution is causing the delay. A fact that has been confirmed by forcing the evaporation of the gas (i.e. extraction with vacuum or bubbling N_2) and the mixture polymerized faster again.

F. Corrective Actions

Currently, the investigation is focused in determining the fine tunning adjustment of the SO_2 concentration in the raw material, a task made in collaboration with the supplier that is performing their own investigation. On the other hand, the optimal transport and storage conditions are being evaluated in order to assess the influence in the SO_2 equilibrium to avoid the modification of the usual polymerization profile.

G. In-vitro Studies

G.1 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.

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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.

G.2 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 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: Xave = 8.7 N & 10.3 N vs. Xave = 20.9 N & 25.0 N.

G.3 Studies related to Skin closure

Two batches of Histoacryl showing unexpected curing behavior at Adhesive Force testing conditions 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.

Test results 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.

(*) 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.

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Risk assessment Conclusion

The initial risk assessment of the incident, considering the preliminary information available on the product characteristics, led us to a conservative approach, not accepting the potential risk for patients. Nevertheless, a deeper investigation has led us to update the risk assessment of the product and now the risk has been considered acceptable.

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

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.

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According to the results of the root cause investigation further code-batches are impacted with the same issue as the products already recalled from the market. These batches will be recalled too as per Regulatory Risk because they do not fulfil the product specifications. Although the risk is considered acceptable.

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