STATEMENT OF VALIDITY

Statement in response to the inquiry regarding the validity of biocompatibility studies performed for PA2200 MP

Customer:	EOS GmbH Robert-Stirling-Ring 1 82152 Krailling/Munich Germany
Product:	PA2200 MP
Studies:	See Table 1 on page 5
Question:	**Are the reports still valid?**
Statement No.:	020-00235
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Statement

Although several referenced standards and guidelines have been revised, no changes have been implemented which could impact the conclusions given in the single reports as summarized in Table 1.

Evaluation of Referred Standards

Below the individual standards to which reference were made for the studies to be evaluated (see Table 1), were reviewed for changes compared to the currently valid versions of the corresponding standards. In addition, in case of changes, the impact of the changes on the validity of the performed studies was evaluated by the expert.

General Standards

Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (ISO 10993-1)

Revisions of ISO 10993-1 were made in the years 2009 (ISO 10993-1:2009), 2010 (ISO 10993-1 Technical Corrigendum 1:2010) and 2018 (ISO 10993-1:2018).

In general, the current standard places a higher focus on an assessment of the biological safety of a medical device within the framework of a risk assessment according to ISO 14971:2007. Additionally, in the current version of ISO 10993-1 (ISO 10993-1:2018) a greater focus was placed on chemical characterization studies according to ISO 10993-18:2020 of the materials used. Evaluations based upon physical and/or chemical information (e.g., chemical characterization studies) are a prerequisite for a risk assessment and are, therefore, explicit included in the actual assessment table of Annex A. Finally, the current version of ISO 10993-1 requires a comprehensive biological risk assessment of all available data, prepared by an expert.

The categorization of medical devices was in generally not changed in the various versions. However, within the latest version additional definitions for “Non-contacting devices” and “Transient-contacting devices” categories were included.

It has to be mentioned that the product under investigation is a raw material used as a compound of medical devices and is not a medical device itself. Based on the information provided by the sponsor and with regard to the underlying evaluation, the product shall be classified as surface device with long term contact to intact skin. As the “Table A.1 - Endpoints to be addressed in a biological risk assessment” available in the current ISO 10993-1 version differs significantly from the corresponding tables found in ISO 10993-1:2009 version (referenced for the studies under evaluation), physical and/or chemical information is identified as additionally biological endpoint to be considered for PA2200 MP.

As the product is already marketed, the need to perform these additional tests has to be evaluated within a biological risk assessment according to ISO 10993-1:2018.

Nevertheless, the revisions to ISO 10993-1 do not affect the validity of the studies evaluated.

Sample preparation and reference material (ISO 10993-12)

Revisions of ISO 10993-12 were made in 2007 (ISO 10993-12:2007) and 2012 (ISO 10993-12:2012).

The change of the reference standard concerning sample preparation and reference material, ISO 10993-12:2007 (referenced for the studies under evaluation) to latest version ISO 10993-12:2012 was initially reviewed for this statement. It can be stated that there were no major changes in the requirements concerning *in vitro* and *in vivo* sample preparations and reference materials which would influence the conclusions of the studies performed with PA2200 MP.

Additionally, there were no major changes for test sample selection, test sample and reference material preparation, which could influence testing of the PA2200 MP.

Therefore, the revisions to ISO 10993-12 do not affect the validity of the studies evaluated.

Evaluated Reports

In vitro Cytotoxicity Assay (BSL Study 094861)

ISO 10993-5:

The BSL BIOSERVICE Study 094861 was already conducted under the currently valid version of ISO 10993-5:2009.

Therefore, the conclusions made in the test report 094861 by BSL BIOSERVICE GmbH are still valid.

Irritation Test (Intracutaneous Reactivity) (BSL Study 094863)

ISO 10993-10:

Revisions of ISO 10993-10:2002 were made in the years 2006 (ISO 10993-10 AMD 1:2006) and 2010 (ISO 10993-10:2010).

Due to the revision of ISO 10993-10:2010, the number of test animals has been updated from 2 to 3 in the actual guideline for intracutaneous reactivity. In the BSL BIOSERVICE Study 094863 two animals were used showing no signs of irritation for the polar extract of the test item compared to the corresponding control. Very slight signs of irritation were found for the nonpolar extract and the nonpolar reagent control during the entire observation period. Under consideration of these test results it is unlikely that testing a third animal will show irritant effects and the test item will be classified as irritant.

Due to animal welfare requirements (German animal protection law) repeating a study under the requirements of the current standard can only be performed on request of the authority.

Therefore, it is the expert's opinion that the conclusions made in the test report 094863 by BSL BIOSERVICE are still valid.

Test for Sensitization (Local Lymph Node assay) (BSL Study 094864)

ISO 10993-10:

Revisions of ISO 10993-10:2002 were made in the years 2006 (ISO 10993-10 AMD 1:2006) and 2010 (ISO 10993-10:2010).

According to the currently valid ISO 10993-10:2010, the implementation of the test for sensitization (Local Lymph Node assay) has not changed.

OECD 429:

An adaption of OECD 429:2002 was made in the year 2010. The changes include a set of Performance Standards (PS) that can be used to evaluate the validation status of new and/or modified test methods that are functionally and mechanistically similar to the LLNA. No significant changes regarding the experimental set up were obtainable.

Therefore, the conclusions made in the BSL BIOSERVICE test report 094864 are still valid.

Conclusion

Although the international standards of the referenced guidelines have been revised, no changes have been implemented which could impact the conclusions given in the single reports. Therefore, it is concluded that the single reports, as listed in Table 1, are still valid.

Therefore, the conclusions made in the test reports 094861, 094863 and 094864 by BSL BIOSERVICE GmbH are still valid.

Planegg, January, 26, 2021

signed by:
Marcel Dörkes
on: 2021-01-26
with:
digiSeal® by secrypt

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Table 1: Studies reviewed

Test	Referred Standards	Current Valid Standards	Test Material	Test Report No.
***In Vitro* Cytotoxicity Assay – GLP**	ISO 10993-1:2009 ISO 10993-5:2009 ISO 10993-12:2007	ISO 10993-1:2018 ISO 10993-5: 2009 ISO 10993-12:2012	PA 2200 Reused powder (50% virgin + 50% recycled powder from EOSINT P System)	BSL Study 094861
Irritation Test (Intracutaneous Reactivity) – GLP	ISO 10993-1:2009 ISO 10993-10:2002 + Amendment 1:2006) ISO 10993-12:2007	ISO 10993-1:2018 ISO 10993-10:2010 ISO 10993-12:2012	PA 2200 Reused powder (50% virgin + 50% recycled powder from EOSINT P System)	BSL Study 094861
Test for Sensitisation (Local Lymph Node Assay – LLNA) – GLP	ISO 10993-1:2009 ISO 10993-10:2002 + Amendment 1:2006) ISO 10993-12:2007 OECD 429:2002	ISO 10993-1:2018 ISO 10993-10:2010 ISO 10993-12:2012 OECD 429:2010	PA 2200 Reused powder (50% virgin + 50% recycled pow der from EOSINT P System)	BSL Study 094864