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Certificate

This is to certify that the below mentioned production line can be utilized in GMP regulated environments according to EU-GMP Guideline – Annex 15 and PIC/S Guideline PI 006-3.

Product line:	**Weighing platforms of the series PBA639 and PBD659**
Manufacturer:	Mettler-Toledo (Albstadt) GmbH Unter dem Malesfelsen 34 72458 Albstadt Germany

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Content

1 Description of the product line

1.1 Weighing platform PBA639 and PBD659

The weighing platforms of the series PBA639 and PBD659 consist of a substructure and a load plate available in an open or a closed design. Open platter is only available for size QA, A, QB, BB and B.

The substructure (see Figure 1) is composed of a round tube frame structure, four leveling feet with adjustable screws, impact and overload protection, and a sealed load cell located in the center that is rated IP68 and IP69k. The load cell can be selected in two different versions, analog with the series PBA639 or digital with the series PBD659. [1].

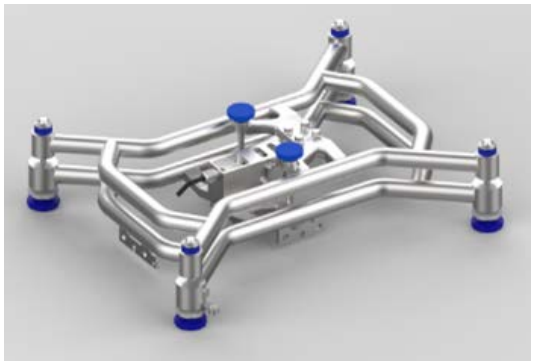

Figure 1: Substructure weighing platform PBA639/PBD659 [1].

The frame structure as well as the load cell housing are made of stainless steel 1.4301 (AISI 304). To ensure optimal cleaning, the weighing platform has rounded edges and easily accessible flat surfaces.

In the basic version, a closed load plate is supplied (see Figure 2 (A)), which is available in two stainless steel versions: type 1.4301 (AISI 304) or 1.4401 (AISI 316).The surface roughness of the load plate Ra is ≤ 0.8 µm.

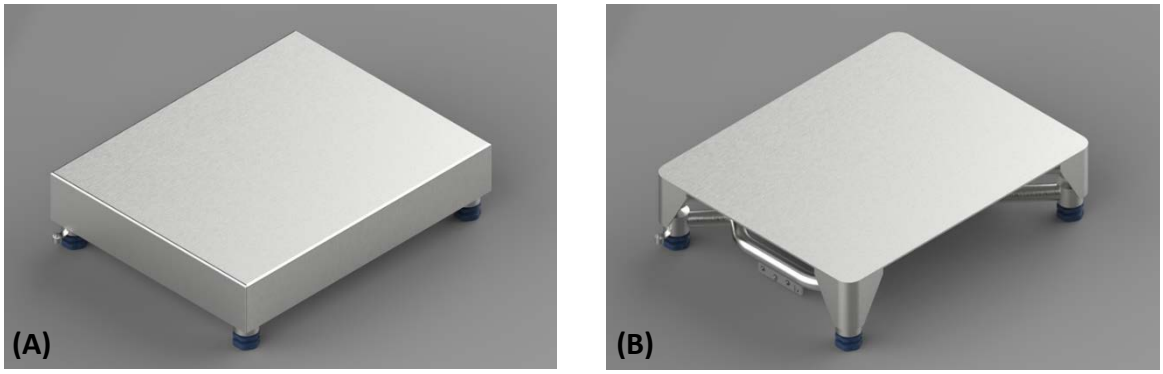

Figure 2: (A) Weighing platform PBA639/PBD659 with closed load plate [1]. (B) Weighing platform PBA639/PBD659 with opened load plate [1].

Due to the closed design, contamination of the substructure can be prevented. To clean the substructure, removing the load plate is possible. The open load plate design (Figure 2 (B)) is made of 1.4401 (AISI 316) stainless steel and provides direct visibility of contamination and easy cleaning. The weighing platforms are available in seven different sizes: QA, A, QB, BB, B, BC or CC size. [2]

2 General requirements for the equipment according to EU-GMP Guideline, Part I

In the EU-GMP Guideline, part I, it is stated: "*premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products.*" [3].

Therefore, the product lines PBA639 und PBD659 described under 1 are tested for GMP conformity according to the following criteria:

- Construction:
  - Suitable for the intended use
  - Possibility of thorough cleaning
  - Avoidance of cross contamination
  - Minimization of errors while working
- Maintenance and service

The load plates of the weighing platforms PBA639 and PBD659 are in contact with the product. In order to assess conformity with GMP regulations, a risk analysis was carried out in accordance with ICH Q 9 [4], using a "fishbone diagram". To check cleanability, a microbiological smear test was performed, as well as a visual check of cleanability according to the "Visually Clean" criteria [5]. The verification of the cleaning success is described in the EC GMP Guideline Annex 15 [6], the PIC/S Guideline PI 006-3 [7] and in the "FDA Guide to Inspections of Validation of Cleaning Processes" [8].

3 Cleaning validation

3.1 Basic data for cleaning validation

The closed load plate (Figure 2 (A)) of the product lines PBA639/PBD659 (B-size: 400x500mm) and the substructure (serial number: 7289165965) were used for cleaning validation. The cleanability of the surface and the cleaning validation are tested using predefined acceptance criteria. After cleaning, no microbial residues may be present and the surface must be visually clean. The aim of the cleaning validation is the complete cleanability of the surface that comes into contact with the product. In case of the weighing platform, this is the load plate. The substructure of the weighing platform is not in contact with the product. Contamination can be easily cleaned off after removing the load plate.

3.2 Performance and results of cleaning validation

The following types of tests are performed on the load plate of the weighing platform to check cleanability:

- Testing of microbial contamination for molds, bacteria and yeasts
- Visual control of cleanability

The sampling of the microbiological contamination is carried out by means of a smear test on the load plate of the weighing platform. For visual control of cleanability, a fluorescence test is performed. This is to ensure that no visible contamination is present after cleaning.

3.2.1 Smear test

In order to test the cleanability of the load plate, a smear test is carried out before and after cleaning. For this purpose, culture media from SGS Analytics & Services Germany GmbH are used. A smear test consists in each case of a duplicate sample, i. e. two different culture media for checking the bacteria as well as the molds and yeasts. To verify the repeatability of the results, the duplicate samples are taken from two different test points (shown in red in Figure 3) on the surface of the load plate.

Figure 3: Sampling for the smear test on the load plate of the product lines PBA639/PBD659 with test points 1a, 1b, 2a, 2b

The first sampling takes place on the uncleaned load plate. After sampling, the surface is cleaned. This is done on the surface with the cleaning agent Sepithol from Steris. After a one-minute exposure time, the cleaning agent is wiped off with paper towels and the load plate is aired for 5 minutes. Then, again, two swab duplicate samples are taken from each test point shown in Figure 3. The four duplicate samples were sent to the laboratory SGS Analytics & Services Germany GmbH in Essen and examined there.

Result of the smear test:

The results of the smear tests show significant contamination with a high total bacterial count at both test points before cleaning of the load plate. After cleaning, there was a clear reduction in the total bacterial count. Accordingly, a very good cleanability of the load plate in contact with the product (product lines PBA639/PBD659) could be proven with the smear test.

3.2.2 Fluorescence test

The fluorescence test is intended to check the cleanability of the surface by visual inspection. Riboflavin (company: Sigma-Aldrich), which fluoresces yellow under UV light, is used as the test sample. This is dissolved in water and distributed on the surface of the load plate to simulate contamination. With the aid of a UV lamp, the contamination is visually inspected and documented photographically. The load plate is then cleaned in a standard dishwasher. To confirm the cleaning success, the surface of the load plate is examined for fluorescent residues of riboflavin using the UV lamp and also documented photographically.

Result of the fluorescence test:

After cleaning the load plate, no residues of riboflavin are under UV-light visible, thus the load plate could be successfully cleaned of all residues (see Figure 4). The product contacting load plate of the product lines PBA639/PBD659 thus fulfills the "Visually Clean" criteria with regard to cleanability.

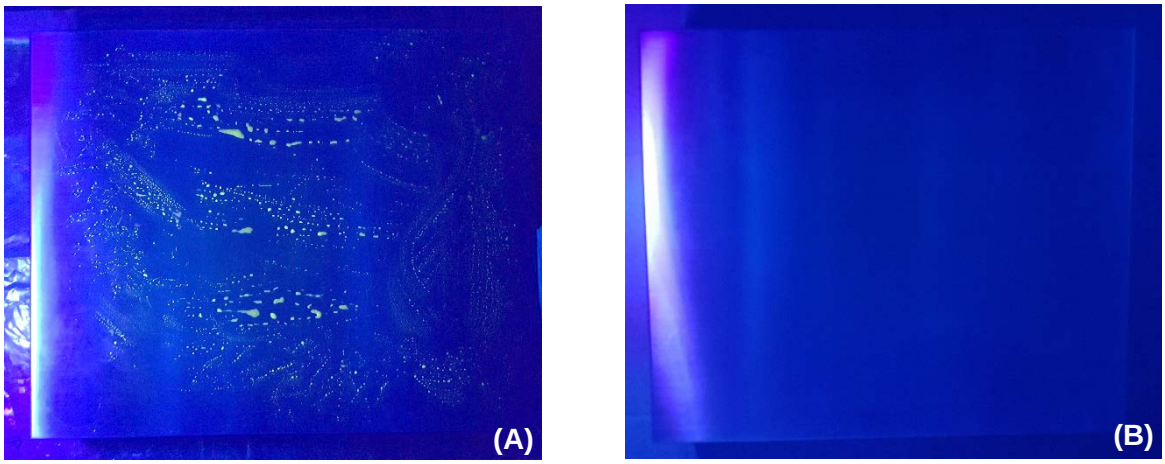

Figure 4: (A) Surface contamination of the load plate (product line PBA639/PBD659) with riboflavin under UV light. (B) Surface of load plate (product line PBA639/PBD659) after cleaning under UV light.

4 Review of the documentation

The documentation of the product lines PBD659 and PBA639 is extensive. A detailed description of the weighing platforms with design drawings in English exists. The materials used are described in detail.

5 Summary assessment of GMP compliance

The product lines PBD659 and PBA639 are suitable for GMP-compliant work according to EC GMP Guideline Annex 15 [6] and PIC/S Guideline PI 006-3 [7]. The following parameters were tested: design under the special aspects of cleanability and the suitable design for intended operations as well as sufficient documentation.

6 List of References

[1] Mettler Toledo, Albstadt: "Product Introduction".

[2] Mettler Toledo, Albstadt: „Weighing Platforms - PBA639/PBD659“.

[3] German Federal Ministry of Health, Guide to Good Manufacturing Practice, Part I, 2008.

[4] European Medicines Agency, ICH, Quality Risk Management - Q 9, 2015.

[5] Maas & Peither, GMP Advisor, GMP Publisher Schopfheim, Chapter 8 E.5, 2016.

[6] European Commision, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use - Annex 15: Qualification and Validation, 2015.

[7] PIC/S, Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-sterile Process Validation, Cleaning Validation, PI006-3, 2015.

[8] U.S. Food and Drug Administration, FDA Guide to Inspections of Validation of Cleaning Processes, 1993.

[9] Maas & Peither, GMP Advisor, GMP Publisher Schopfheim, Chapter 19 E.3, 2020.

7 List of Figures