Certificate

We hereby certify, that the below mentioned production lines meet

all GMP-guidelines, EG –GMP-Annex 15 guideline
and PIC/S guideline PI 006-2 requirements.

Product lines:	**D-, PUA, PTA45-, K-, M and PFA579**
Manufacturer:	Mettler-Toledo (Albstadt) GmbH Unter dem Malesfelsen 34 72458 Albstadt Germany

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Prof. Dr. Ingrid Müller

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1. Description of the product lines

D-Line

The D-Line consists of 6 different product families

1. DN Line Bench scales
   use of DMS cell (strain gauge)
   platform sizes [mm]: 240x300, 300x400, 400x500, 500x650, 600x800
   weighing capacity [kg]: 6, 15, 30, 60, 150, 300, 600
2. DB-DCC
   the DB-DCC-Line bench scales are built up hybrid – with a DMS-measuring cell and a lever arm system.
   Platform size [mm]: 400x500, 600x800, 800x800, 1000x800
   Weighing capacity [kg]: 30, 60,150,300,600
3. DN- Line floor balances
   Suitably for floor-mounted or pit-mounted installations
   Use of 4 DMS measuring cells
   platform size [mm]: 1250x1000, 1500x1250, 1500x1500, optional size
   weighing capacity [kg]: 300, 600, 1500, 3000
4. PTA45...
   Pallet balances for weighing pallets simply
   Use of 4 DMS measuring cells
   platform size [mm]: 1260x600, optional size
   weighing capacity [kg]: 300, 600, 1500, 3000
5. DU Line / PUA579…
   extreme flat moveable balances
   Use of 4 DMS measuring cells
   platform size [mm]: 850x850, 1500x1250, optional size
   weighing capacity [kg]: 300, 600, 1500, 3000

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6. DRF/DSF Line

   flexible heavy scales, up to 3 modules,

   suitable for floor-mounted and pit-mounted installations.

   Use of 4 DMS measuring cells for each module

   platform size [m]: 1,5 - 2 x 1,5 - 6

   weighing capacity [kg]: 3000, 6000, 12000 (only DSF)

K-Line

The K-Line contains bench- and floor scales.

Hybrid construction, electromagnetic strength compensation cell and lever arm system.

Calibrating capable resolution: up to 15000 / 32000e

Platform size [mm]: 280x350mm to 2000x1500mm

Weighing capacity [kg]: 15 kg to 6000kg

M-Line

The M-Line contains bench- and floor scales.

Hybrid construction - digital DMS measuring cell and lever arm system.

Calibrating capable resolution: up to 3x3000e multi interval

Platform size [mm]: 280x350mm to 1500x1500mm

Weighing capacity [kg]: 15 kg to 3000kg

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PFA579 line

The line “PFA579” consists of floor scales, which can be upgraded and configured.

They can be installed as floor-mounted scales or as pit-mounted scales.

The four measuring cells (DMS measuring cells) are based on strain gauges.

The PFA579 line consists of stainless steel, type AISI 304/316.

Weighing range [kg]:	300-3000 kg
Platform sizes:	between 700x400 and 2000x1500 mm

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2. General requirements for balances

Balances have to show the suitable measurement range and the required precision (EC-GMP guide[1], chapter 3.40).

They have to be calibrated regularly, which has to be documented (EC-GMP guide, chapter 3.41).

The permitted tolerance must be provided for the respective weighing capacity,

by consideration of the measuring inaccuracies, i.e. the still tolerated deviation of the debit value.

Working with raw materials, the equipment and the utensils used have to meet the requirements for surfaces in pharmaceutical production.

According to § 211.65 “Construction of the equipment”[2] of the FDA: *„(a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.”*

The cleaning ability is confirmed by the cleaning validation. Established cleaning instructions are necessary as a prerequisite for a cleaning validation.

The amount of permitted residuals whether active pharmaceutical ingredients or cleaning agents, is dependant on the preliminary manufactured product. These include the derivative product and the lot size of the derivative product. A first, general statement for not critical products can be made with the criteria "visual clean". According to the literature[3], backlogs of 375 µg per 100 cm² are no longer visible.

[1] EC-GMP guide, chapter 3.40

[2] USA 21 CFR Part 211

[3] Buscalferri et.al., Pharmind 62, Nr. 6 (2000)

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3. Appraisal criteria for an optimal cleaning

General

In principle, those parts of equipment, which come into contact with the product, have to be cleaned well. Regarding the balances, these parts are the load plates.
Both the FDA inspection guideline for cleaning validation and the PIC guideline PIC/S 006-2 name the visual criteria as one possible acceptance criteria to appraise the cleaning success.
The balances of the product line D-, PUA, PTA45-, K-, M Line and PFA579 were subjected to a qualified examination regarding "cleaning ability".[1] This means that the balances of the product lines D-, P- K-, M and PFA579 must be free of visible residuals after cleaning. As a basis for this examination the works of Buscalferri, F., Assignation of the visibility limit of pharmaceutical active agents (“Bestimmung der Sichtbarkeitsgrenze von pharmazeutischen Wirkstoffen”), master thesis, Albstadt-Sigmaringen University, course of studies pharmaceutical technology (1999) and Fourman, G. L., Mullen, Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations , Pharm. Technol. 17 (4), 54 (1993) were used.

[1] The examinations were carried out by Prof. R. Ziegler

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Procedure

A granulated material, which was coloured with Erythrosine, was used as a sample. The examinations[1] were carried out according to the "visually clean" criteria (please see "GMP Berater" 8E (11)). First the load plates of the product lines D-, PUA, PTA45-, K-, M and PFA579 were polluted, following by a cleaning step. A cleaning agent (P3-cosa PUR 80 Manufacturer: Ecolab GmbH & Co. OHG, Düsseldorf), which is commonly used in pharmaceutical production was taken and feigned according to different pollution degrees.
The cleaning success was then appraised visually.
In addition, a cast test was carried out before and after the cleaning to determine the complete microbial count.
The exact data can be taken from the SOP for cleaning and from the test report. These results show clearly, that the depletion degree meets in principle the hygienic requirements. In principle the depletion degree is dependent on the examined material and the specific requirements of the examination.

Results

In regard to the cleaning, the load plates of the product lines, D-, PUA, PTA45-, K-, M and PFA579, correspond to the visually clean criteria. The cast test for the determination of the complete microbial count showed a significantly lower complete microbial count after the cleaning.

[1] These experiments were performed by Prof. Dr. R. Ziegler

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Summary

The balances and terminals of the product lines, D-, PUA, PTA45-, K-, M and PFA579, are GMP-compliant. The cleaning of the parts, which come in contact with the product (load plate), has to be carried out well. There aren't any heavily accessible places in which dust could accumulate. The load plate is removable, so that the cleaning of the parts which are not in contact with the product is guaranteed.

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4. Appraisal factors for qualification

General

The PIC/S guideline PI 006-2 and the EG-GMP guide Annex 15 mention principles for qualification and validation.
Every machine or equipment which directly or indirectly influences the quality of the product shall be qualified. The machine or equipment shall be designed in agreement with the prevailing GMP guidelines. The machine shall be installed in agreement with the design specification and the functions shall be checked with the available documentation (functional qualification).

Procedure

The available documentation of the Mettler Toledo product lines, D-, PUA, PTA45-, K-, M and PFA579, was checked to the effect of whether design qualification, installation qualification and functional qualification are feasible.

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Results

The documentation of the Mettler Toledo product lines, D-, PUA, PTA45-, K-, M and PFA579, is very detailed. Also an exact description of the balances with design drawings is available. The materials used are described precisely.
GMP-relevant documents are available (e.g. inspection certificate, CE-mark). Particulars regarding the maintenance are furnished.

Summary

The documentation of the manufacturer of the Mettler Toledo product lines, D-, PUA, PTA45-, K-, M and PFA579, is written in a very detailed way and offers the necessary conditions for the execution of qualification, as it is demanded by EG-GMP guide Annex 15 and PIC/S guideline PI 006-2.

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