Steinbeis-Transferinstitut
Life Sciences Technologies
der Steinbeis University Berlin

Certificate

We hereby certify, that the below mentioned production lines meet

all GMP-guidelines, EG –GMP-Annex 15 guideline
and PIC/S guideline PI 006-1 requirements.

Product lines: **4er Serie (BBA4... / BBK4... / IND4...)**

Manufacturer: Mettler-Toledo (Albstadt) GmbH
Unter dem Malesfelsen 34
72458 Albstadt
Germany

Tübingen, 30.05.2005

Prof. R. Ziegler

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1. Description of the product lines

Compact balances of the 4 series: BBA4... / BBK4...

Industrial compact balances with high-quality aluminium pressure die-casting case and chrome nickel steel scale. The product line stands out due to different application steps, weighing capacity and interface options. Calibrating capable models of the precision classes II (BBK4...) and III (BBA4...) as well as protection kind of IP 65 of (EN60529) are available. All models fulfil the highest EMV industry standards, in accordance to German chemistry (EN61326-1 class B, EN61000-3-2, EN61000-3-3, EN61326-1) as well as the electrical safety regulations in accordance to EN61010 1.

Terminal line of the 4 series: IND4...

Industrial compact balances consisting of high-quality aluminium pressure die-casting-operating unit and a weighbridge made of powder coated steel with a pan made of chrome nickel steel* for use in dry up to damp surroundings (in accordance to protection class of IP 65* (EN60529)).
The product line stands out due to different application steps, weighing capacity and interface options. Calibration capable models of the precision class III to OIML are available.
All models fulfil the electrical safety regulations in accordance to EN61010- 1 as well as the norms for not independent balances in accordance to EN45501.
*depending on execution

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2. General requirements of balances

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

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

The permitted tolerance must be provided under consideration of the measuring inaccuracies, i.e. the still tolerated deviation of the debit value, for the respective weighing capacity.

The equipment used at the handling with the raw materials and utensils must meet the requirements for surfaces in the pharmaceutical production.

The FDA writes according to § 211.65 construction of the equipment: *„(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 clean ability is confirmed by the cleaning validation. Established cleaning instructions are necessary as a prerequisite for a cleaning validation

The at most permitted spreading amount of active ingredients and cleaning agent is depending on the preliminary product, the derivative product and the lot size of the derivative product. A general statement for not critical products can be made with the criteria "visual clean". Due to respected and in the literature described tests a quantity in backlog of 375 µg per 100 cm^2 is no longer visible.

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3. Appraisal factors for an optimal cleaning

General

In principle, the parts which come in contact with the product, these are the burden plates of the balances, have to be cleaned well.

Both the FDA inspection guideline for cleaning validation and the PIC guideline PIC/S 006-1 name the visual criteria as acceptance criteria to appraise the cleaning success.
The balances of the product line / terminals of the 4 series (BBA4... / BBK4... / IND4...) were subjected to a qualified examination regarding "clean ability". Therefore the criteria „visually clean“ was used. This means that the balances of the products BBA4... / BBK4... / IND4... must be free of visible residua 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.

Proceeding

As examination sample there was chosen granulate, that was colored with Erythrosine. As a basis the criteria “visually clean” (please see “GMP Berater” 8E (11)) was consulted. Different pollution degrees were feigned, the burden plates of the products BBA4... and BBK4... were polluted and then cleaned with a common cleaning agent (P3-cosa PUR 80 Manufacturer: Ecolab GmbH & Co. OHG, Düsseldorf), used in the pharmaceutical production.
The cleaning success was then appraised visually.

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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 the test report is also obvious that the depletion degree which is dependent on the examination material and the specific requirements of the examination meets in principle the hygienic requirements.

Results

Regarding the cleaning the burden plates of the products BBA4…/BBK4… 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.

Summary

The balances and terminals of the 4 series are GMP-compliant. The cleaning of the parts, which come in contact with the product (burden plate), has to be carried out well. There aren't any heavily accessible places in which dust could accumulate. The burden 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 criteria for a qualification

General

The PIC/S guideline PI 006-1 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

Proceeding

The available documentation of the Mettler Toledo 4 series (BBA4... / BBK4... / IND4...) was checked to the effect whether a design qualification, installation qualification and functional qualification is feasible.

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Results

The documentation of the product the Mettler Toledo 4 series (BBA4... / BBK4... / IND4...) is very detailed. A detailed description of the balances with design drawings is available. The used materials are described in detail.
GMP-relevant documents are available (e.g. inspection certificate, CE-mark). Details on the maintenance are listed.

Summary

The documentation of the manufacturer of the Mettler Toledo 4 series (BBA4... / BBK4... / IND4...) is very detailed and offers the necessary conditions for the execution of a qualification as it is demanded by EG-GMP guide Annex 15 and PIC/S guideline PI 006-1.

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