Cleaning validation for blister packaging machines in an Austrian pharmacy

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ABSTRACT

Objectives Our pharmacy works in accordance with the Good Manufacturing Practice in the area of multidose individual blister repackaging. This required validating the cleaning procedure of the blister machines accounting for the characteristics of our setting and investigating worst possible production scenarios.

Methods Visual clean: After machine cleaning we inspected surfaces for visible residues. Cross-contamination: A tablet vulnerable to contamination was analysed after blister packaging for residues of a medication with high contamination risk using. Critical medications in the machine were identified by their dust formation potential. Placebo tablets were blister-packaged and analysed for residues of these critical medications using mass spectrometry. We assessed pharmacological relevance of contamination from these two analyses by the dose criterion. Validity of results: Comparing production conditions and technical construction of the blister machines, validity of the validation results for the whole setting was investigated.

Results After cleaning no residues were visible on the machine. No contamination was detected on the vulnerable tablet. In 80% of 280 analysed placebo tablets contamination was not measurable or below 1% of the cut-off limits according to the dose criterion, the highest value being 8.5%. Production volume and cleanability were comparable in the other machines.

Conclusions Blister machine cleaning was successfully validated: visual cleanliness was achieved; contamination values were clearly below the cut-off limits, ruling out relevant cross-contamination of copackaged drugs. The results proved valid for the whole site. The study contributes evidence to safety and quality of blister repackaging and may serve as reference for similar settings.

INTRODUCTION

In Austria, blister repackaging is regulated by the Medicinal Products Act (Arzneimittelgesetz, AMG).¹ It means the individual isolation and mechanical repackaging of medicinal products in rations for individual patients. In many countries, blister repackaging is already well established. In Europe, it is practised to a large extent, for example, in the Netherlands and in the Scandinavian countries, where blister centres supply up to several thousands of patients. Also more and more hospital pharmacies offer this service. The key advantages are: increased safety of medications (pharmaceutical check of the medication plan, low mechanical error ratio of the blister machines), economisation (release of resources among nurses and caregivers, reduced medication waste) and improved therapy compliance.^{2–6}

Blister repackaging was set up in the pharmacy of the Barmherzige Brüder Hospital in Linz in 2004. The continuously increasing performance of currently about 2200 supplied beds in hospital and nursing homes has meant (according to §62 and 63 AMG) that production since summer 2011 has been carried out according to the Good Manufacturing Practice (GMP)⁷ and is audited by the Austrian Agency for Health and Food Safety.⁸

A key requirement of GMP-compliant production is a cleaning validation, which confirms the effectiveness of equipment cleaning, especially of product contact surfaces.⁹ Therefore, in the case of blister repackaging, the cleaning of blister machines is particularly relevant. Validation of the cleaning process should take into account the operational circumstances (the workload of the machines or range of production, the type and quantity of packaged medicines, formation of abrasion dust, etc) and deal with the risks of one's setting based on the worst possible circumstances that might occur during production. Acceptance criteria for the validation must be defined in advance.

In our pharmacy, two FDS-330 blister repackaging machines from the manufacturing company Baxter were used in 2011. In 2014, one FDS-330 was replaced by the next generation machine, the Proud model.¹⁰

Our aim was to validate the long established cleaning procedure for the blister machines in our pharmacy. We focused on cross-contamination by drug abrasion, which presents the highest risk. Microbial and particulate impurities are regarded as less critical, especially in view of the controlled environmental conditions (clean room classification grade D) and the type of product (solid oral medication).

In the manufacture of pharmaceutical products three criteria for carry-over of product residues are well established:^{9 11}

- No more than 0.1% of the normal therapeutic dose of any product appears in the maximum daily dose of the following product (dose criterion).
- No more than 10 ppm of any product appears in another product.
- No quantity of residue is visible on the equipment after cleaning procedures.

Notably, GMP guidelines regard visual inspection (c) only as part of the cleaning validation (Eudralex Annex 15).^{12 13}

For application of these cross-contamination tests in the context of blister repackaging, little information is available in the literature.^{14 15} Therefore, distinct scenarios (classification of abrasion, visual and analytical methods) were developed for our

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setting assessing the most critical situations that occur in real production conditions.

The main aim of the study was to validate our cleaning procedure. A priori, we defined acceptance requirements that had to be fulfilled:

- ▶ Conformance to the visual clean criterion;
- ▶ Conformance to the dose criterion;
- ▶ Validity for the whole setting.

The cleaning validation therefore sought to answer the following four questions:

1. Is visual cleanliness of the blister machine achieved by the established cleaning procedure? = visual clean.
2. Is a little-used drug with low active substance content contaminated by the dust of a copackaged drug with high active substance content used a lot in the machine, which presents the greatest risk of contamination and the most critical effect? = WCS A (worst case scenario (WCS) A).
3. Which are the highly dust-producing drugs in our setting and can residues of these high-abrasion drugs be detected in coblister-packaged placebo tablets? = WCS B.
4. Are the results from the validation process transferable to the whole setting?

The WCSs investigate carry-over of product residues and judge therapeutic relevance for patient safety by the dose criterion. Visual clean, WCS A and B were designed to demonstrate a before-and-after effect of the cleaning status of the machine.

The validation process was set up for one FDS machine, which operates under the 'worst possible' conditions in our setting, intending validity and transferability of the results to the other FDS machine and later to the Proud model. Furthermore, the WCSs were based on the biggest and therefore 'riskiest' usual weekly production order, as this is where most contamination is likely to arise.

Further aims of the study were that

- ▶ The high safety standards provided by patient individual blister packaging should be confirmed;
- ▶ The results should be applicable and representative for other (similar) sites and
- ▶ Scenarios and methods might present an input for colleagues facing similar challenges.

METHODS

Starting points: cleaning procedure, reference machine and riskiest order

The cleaning validation was based on the cleaning routine for the blister machines that had long been established in our pharmacy and was based on Baxter's cleaning procedure for FDS-330 and the user manual. The cleaning procedure (table 1) includes sites, mode, interval and detergents of cleaning and takes into account:

- ▶ Accessibility: cleanability of difficult-to-reach sites (like sashes) only by maintenance engineers during servicing; reachability with a vacuum cleaner;
- ▶ Compatibility of machine parts with cleansing agents;
- ▶ Years-long experience of the level of soiling of machine parts at various time intervals (day, week, quarter) and of drugs producing high amounts of dust;
- ▶ Risk assessment: identification of product contact surfaces.

The reference machine for the validation approaches is an FDS machine, equipped with 233 cassette medications, which has the highest packaging volume, the biggest orders, a wide and adequate selection of medication including highly dust-generating drugs repacked in large quantities.

Table 1 Excerpt of the FDS machine cleaning standard operating procedure

Cleaning interval*	Machine parts	Cleaning mode
Before each cassette filling	▶ Cassettes	▶ VC, AC
	▶ Sensors	▶ DC
Every day	▶ Insert of the DTA and DTA filling tray	▶ VC, AC
	▶ Carousel sensors	▶ DC
	▶ Divide ring drawer	▶ VC, WC
Once a week	▶ Small pill hopper	▶ WC
	▶ Large pill hopper	▶ WC
	▶ Inner carousel pill guide	▶ WC
	▶ Triangle plate	▶ SB
	▶ Heat rollers	▶ HB, DC
	▶ Outer housing of the blister packaging machine	▶ AC
	▶ Inner housing of the blister packaging machine	▶ VC, AC
	▶ Sash entries and motor bases of highly dust raising drugs	▶ VC, SB, AC
	▶ Bucket assembly	▶ AC
	▶ Drum interior	▶ WC
Once per quarter	▶ Sash entries and motor bases of little dust raising drugs	▶ VC, SB, AC
	▶ Sash endings at the drum	▶ VC, AC
	▶ Air vent behind machines, inner area of the machine at posterior hatch, floor under machine at the back	▶ VC, AC
	▶ DTA screwed apart	▶ AC
	▶ Sashes	▶ CB

*Additional cleaning activities in case of visible soiling. AC, alcoholic disinfectant soaked cloth (Mikrozid;¹⁶ standard for all possible sites, dries quickly without residues); CB, brush on a cable; DC, dry cloth (during production); DTA, detachable tray adapter; HB, hard brush; SF, soft brush; VC, vacuum cleaner (for coarser soiling); WC, water soaked cloth (for sites not treatable with alcoholic solution, dries slowly).

The biggest weekly production order is a 3-day order for a neuropsychiatric hospital and supplies 560 patients with 14 900 tablets packed in 7500 blister bags (average amounts for first quarter 2011).

Question 1: visual clean

The cleaning procedure was monitored at the routine cleaning intervals (daily, weekly and quarterly) focusing on soiling and dust formation on the various parts of the blister machine. Both employees usually responsible for machine cleaning were assessed at all three intervals. Appropriate time intervals and sufficient cleaning efficiency were to be demonstrated. Microfibre wiping cloths¹⁷ with a dust absorbing structure helped to visualise soiling by swabbing the surfaces. Since most medications are white or of other light colours, we chose dark blue cloths that show dust of these medications easily. Visual inspections of the machine parts before and after cleaning were carried out by the same person. The approach was photographically recorded.

Question 2: WCS A Protocol

WCS A was based on Depakine 500 mg (valproic acid) and Euthyrox 25 µg (levothyroxine) that display the highest and lowest value, respectively, from the number of repackaged tablets multiplied by active substance content. Nine hundred and fifty Depakine followed by 20 Euthyrox tablets were blister-packaged (series 1). The number of 950 Depakine and 20 Euthyrox represent the average quantities of these tablets in the

biggest weekly order. After a standard daily cleaning procedure, repackaging was repeated (series 2) to establish the differences in resulting contamination.

The tablets were sent coded to Professor Freissmuth of the Institute of Pharmacology, University of Vienna (<http://www.meduniwien.ac.at/hp/zpp/institute-abteilungen/zentrum/>) to check as to how much valproic acid was recovered from Euthyrox 25 µg tablets. The contamination limit was set to 1.4 mg of valproic acid (=1/1000 of the daily dose for a patient weighing 70 kg) to be packed onto the maximum therapeutic daily dose of Euthyrox (12 tablets), that is, 120 ng per tablet.

For this, the tablets were removed from the blister packs and extraction was carried out. The quantity of valproic acid adhering to the Euthyrox tablets was determined using high performance liquid chromatography (HPLC). Per series 12 tablets were analysed—the analysis being blinded—the rest retained for investigation of any queries that might occur. Euthyrox tablets, to which defined quantities of dissolved valproic acid had been added, were used as internal control.

Investigated material

Per series, 2×8 tablets and 1×4 tablets Euthyrox 25 µg tablets were blister-packaged on 5 July 2011, sent to the Pharmacological Institute and received on the same day.

Analysed per series were 8+4 tablets; 8 tablets were retained in accordance with the protocol. The analysis was blinded, that is, the investigating team did not know which of the two series had come into contact with tablets containing valproic acid under what circumstances.

Analysis

Solutions

1. Derivatisation solution: 20 mM 18-Crown-6 ether-18-suspension: 26.5 mg 18-C-6 (1,4,7,10,13,16-hexaoxacyclooctadecane—Sigma, item no.: C-5515) was replaced with 5 mL acetonitrile and 50 µL K₂CO₃ (1 g/mL dissolved in ultrapure water) and treated for 30 min in an ultrasound bath. After that another 5 mL acetonitrile were added. BrMMC solution: 4-bromomethyl-7-methoxycoumarin (Aldrich 235202-1G) was dissolved under light protection in acetonitrile in a concentration of 1 mg/mL.
2. Calibration solution: for producing the stock solution, valproic acid (Sigma, item no.: P-6273) was diluted in a concentration of 1 mg/mL in methanol. Dilutions (in ultrapure water) were produced according to the formula summarised in [table 2](#).
3. Internal standard: undecenylenic acid (Sigma, item no.: U-0375) was diluted with acetonitrile to a stock solution of 0.1 mg/mL. The working solution (=extraction solution; 0.01 mg/mL) was also produced in acetonitrile.

Table 2 Dilution formula for producing the valproic acid standard solutions

Dilution	Concentration	Added quantity (10 µL/tablet) (ng)
Stock solution* 1:100	10 µg/mL=A	100
A 1:2	5 µg/mL=B	50
B 1:2	2.5 µg/mL=C	25
A 1:10	1 µg/mL=D	10

*Valproic acid diluted in a concentration of 1 mg/mL in methanol.

4. Eluent for HPLC: acetonitrile (Roth, item no.: 8825.2 Rotisolv HPLC Gradient Grade) 80: 20 ammonium-acetate (Aldrich, 211-162-9) 25 mM (pH 4.0); wash solution 100% acetonitrile.

Creating the standard curve

Euthyrox 25 µg tablets were used for producing the standard curve. To each Euthyrox tablet, 10 µL of the respective standard were added (containing 100, 50, 25 and 10 ng, see [table 2](#), third column) for the calibration curve and 10 µL water for the blank value and the samples.

Extraction

The tablets to which valproic acid solution had been added for determining the standard curve and the tablets from series 1 and 2 were subjected to extraction as follows:

The tablets were placed in 2 mL Eppendorf pipettes and covered with 0.25 mL extraction solution (acetonitrile, to which 10 µg/mL undecenylenic acid had been added as internal standard). These tablet solutions were shaken for 5 min.

The fluid phase was then transferred to a second reaction vessel and centrifuged (1 min at 14 000 rpm, corresponding to 12 200 g).

Derivatisation

Aliquots of the extraction supernatant (each 0.1 mL out of 0.25 mL) were taken and transferred to Eppendorf reaction vessels, mixed with 0.05 mL 18-Crown-6 ether-18-suspension and 0.1 mL BrMMC solution and derivatised for 30 min at 65°C under light protection. After cooling the samples, 0.1 mL ultrapure water was added. The samples were centrifuged, 0.1 mL removed and injected into the HPLC.

The derivatisation reaction creates an ultraviolet absorbing product (from valproic acid and BrMMC; the derivatisation takes place on the carboxyl group, so undecenylenic acid is suitable as internal standard).

HPLC analysis

The analytical separation of the mixed substances was carried out via a Luna 5µm C18(2) columns (Phenomenex; pore size 100 Å, dimensions 250×4.6 mm) at room temperature (22°C). The eluent was added using computer-guided (ChemStation, Hewlett Packard, 76337 Waldbronn, Germany) Agilent 1100 Pump isocratically with a flow rate of 2.5 mL/min. The samples were automatically injected using a Shimadzu SIL6B autosampler. Detection was carried out using an HP1050 Diode-Array-Detector with a wavelength of 322 nm.

Between the analytical runs a wash stage with pure acetonitrile (6 min followed by a 3 min rebalancing period) was programmed. Control of the facility and evaluation were carried out using ChemStation. The analytical method was validated. The limit of detection was 0.086 ng (defined as 3× SD between blank and signal), the limit of quantification (LOQ) was 0.288 ng (defined as 10× SD between blank and signal) (n=3).

Question 3: WCS B

Identification of highly dust-producing drugs

The cassette medications were systematically monitored and classified regarding their formation of dust. At sash entries of all cassettes in the machine, the occurrence of dust was assessed at defined dates:

Date 1: randomly selected point of time, after that, full cleaning of motor bases and sash entries was performed;

Date 2: one day of production after date 1, that is, after approximately 8500 tablets or 3000 blisters;

Date 3: one week of production after date 1, that is, after approximately 38 000 tablets or 15 000 blisters;

Date 4: before the next servicing date, in maximum soiled condition of the machine.

Dust assessments were all carried out by the same person and based on finger swab samples using a dark blue microfibre cloth,¹⁷ rubbing the clothed finger into the entry area of the sash, followed by visual evaluation. Upon the microfibre cloth an investigation section (1.5×2.5 cm) was drawn, to visualise dust formation on motor bases and sash entries. Classifications of dust production ranged from low=no or little amounts of dust (section max. up to one-third soiled) to moderate=medium amounts of dust (section more than about 1/3 but less than two-thirds soiled) to high=section (nearly) fully soiled (about two-thirds to 100%), see figure 1. If classified as moderately or highly dust producing at all four times (date 1–4), a drug was termed ‘high abrasion’. The classification was checked for plausibility accounting for technological aspects and experience with dust formation in our setting.

Protocol for determination of highly dust-producing drug residues on placebo tablets

Professor Schmid of the Clinical Department of Laboratory Medicine, Medical University of Vienna (<http://www.meduniwien.ac.at>) was commissioned to analyse control tablets, that is, placebo tablets,¹⁸ for cross-contamination during routine blister repackaging at our pharmacy for residues of the identified highly dust-producing drugs. These are drugs with a high-abrasion potential from their galenical form, experiences during cleaning and systematic observation of abrasion. Professor Freissmuth of the Pharmacological Institute of Vienna Medical University established the range of concentration below which any significant pharmacological effect could no longer be expected as a result of (possible) residues. It was further established that a limit of at least 1/1000 of a daily dose for adults must definitely be detected on one test tablet, while the detection threshold for the analytical method used must be significantly lower; 1/1000 of a daily dose was chosen as ‘cut-off’ limits (acceptance criteria) and defined the analytical concentration ranges in which the measurements were to be carried out.

Analytical approach

Two HPLC-mass spectrometry systems were chosen for the analyses, routinely used to analyse medicines and drugs, consisting

of Dionex Ultimate HPLC Systems (pump, sampler, column oven) to which were coupled in one case an Agilent 1100 DAD Detector and a Thermo ‘Velos’ Linear Ion Trap Mass Spectrometer, and in the other case a Dionex PDA-100 DAD Detector and a Thermo MSQ Single Quad Mass Spectrometer, both with a heated ESI-Interface. Data evaluation was performed using the Chromeleon 6.8 Integrations System.

Because of the wide polarity of the substances to be examined, a Machery & Nagel Nucleodur Pyramid ODS 2.1×150 mm 3 µm column was used in System 1, and in System 2 a Phenomenex, Kinetex Biphenyl 2.1×150 mm 2.6 µm column with gradient elution.

Chromatographic conditions:

- ▶ Linear dual gradient (with ramp);
- ▶ Running time (RT) 0.0 min: 100% mobile phase A;
- ▶ RT 5.0 min: 90% mobile phase B, then re-equilibration to 100% mobile phase A;
- ▶ RT 9.5 min;
- ▶ Flow rate: 300 µL/min;
- ▶ Column temperature: 60°C;
- ▶ Mobile phase A: ammonium formate buffer 10 mM, pH 3.75;
- ▶ Mobile phase B: 90% acetonitrile/10% ammonium formate buffer 10 mM, pH 3.75.

Sample preparation

The test tablets were ‘dissolved’ in 1.5 mL 75% methanol/water (until they disintegrated), vortexed and treated in the ultrasound bath for 15 min. They were then diluted with 0.5 mL H₂O and treated in the ultrasound bath again for 10 min. After the sediment had been deposited, 300 µL was transferred into a filtration injection flask (Whatman) and 10 µL of the filtration supernatant was injected into the HPLC.

The calibration range for the quantitative evaluation (LOQ) was established with 50% of the cut-off value of the individual drugs, whereby a precision and accuracy of minimum <15% was obtained for all drugs.

In spite of essentially higher cut-off limits, semi-quantitative evaluations were carried out for all drugs up to 0.1–1% (minimum 1/100) of these limits (with less precision), as the measurement approach allowed a significantly higher measurement sensitivity.

Sample descriptions

Sampling took place in July 2014. While processing, the biggest order placebo tablets, filled into a cassette in the upper part of

Figure 1 Microfibre cloth for finger swab test, upon which an investigation section had been drawn to visualise dust formation on motor bases and sash entries. Classifications of dust production—according to the definition in the methods section—ranged from low (left), to moderate (middle), to high (right).

the machine, were blister-packaged in two series with in each case 7×20 blister-packed placebo tablets:

One series was repackaged before the servicing date, that is, in 'maximum dirty' state of the machine (V-Series) and one after the quarterly 'maximum' cleaning (N-Series).

Groups were defined within the series:

Test 1=before batch start (machine completely cleaned);

Test 2=after about 3000 tablets;

Test 3=after about 6000 tablets;

Test 4=after about 9000 tablets;

Test 5=after about 12 000 tablets;

Test 6=after the batch was completed (machine not cleaned);

Test 7=after the batch was completed (machine thoroughly cleaned).

Question 4: transferability of results to other machines

To check, if results from the reference FDS machine are representative for the second machine, that is, the second FDS and its later replacement, the Proud model, we compared:

- ▶ Size of production: order sizes, drug composition and volumes of repackaged tablets (overall and three most frequently blister-packaged drugs);
- ▶ Dust formation according to visual judgement at standard cleaning intervals (daily, weekly, quarterly);
- ▶ Technical construction;
- ▶ Cleanability of the machine parts.

RESULTS

Question 1: visual clean

Inspection of the machine parts before cleaning showed visually detectable soiling at the daily, weekly and quarterly cleaning interval. Medication dust—isolated or as thin layer—was visible. No dust aggregations were seen. Discrete drug fragments were found on horizontal surfaces. After cleaning, the machine parts were visually clean, that is, free from residues (larger particles, dust, discolouration, cloudiness). The results were independent of the employee carrying out the cleaning.

Question 2: WCS A

Blank value

To check the validity of the analytical process, Euthyrox 25 µg tablets were examined, to which only water (10 µL; as vehicle for the addition of valproic acid) had been added. With these tablets, we neither observed a peak at the retention time of valproic acid (or valproic acid–BrMMC derivate) nor at that of the

internal standard (of the undecenylate–BrMMC derivate) (figure 2).

Standard curve

Valproic acid was added in increasing quantities (10, 25, 50 and 100 ng) to Euthyrox 25 µg tablets; as a result, the tablets were subjected to extraction in the presence of the internal standard with acetonitrile, the supernatant converted with BrMMC and the reaction products separated using HPLC. The relevant chromatograms showed: after the addition of 10 ng valproic acid to one tablet Euthyrox this quantity was reliably detected. The peak at 3.66–3.74 min corresponded to the retention time of the valproate–BrMMC derivate, the peak at 6.14–6.39 min to the retention time of the undecenylate–BrMMC derivate.

A calibration curve for valproic acid was established: The quotient of peak heights of analyte (valproate–BrMMC derivate) and internal standard was calculated and plotted against the quantity of valproic acid added to the tablets. A linear dependence was observed in the relevant graph. The correlation coefficient of this calibration curve was >0.99.

Examination of tablets sent

Neither in tablets in series 1 nor in tablets in series 2 was there evidence of valproic acid. Representative chromatograms are shown in figure 3.

Question 3: WCS B

Dust classification (table 3) identified 29 drugs, which at all four times produced moderate or high abrasion. The results from this systematic classification matched (a) technological considerations that capsules and coated tablets are not dust-forming types of medicinal products^{19–21} and (b) our long-standing experience including cleaning and filling the machines concerning the dust-producing potential of the cassette medications.

The analysis, actually planned for 2011, was delayed due to organisational difficulties. The packaging of the placebo tablets took place in summer 2014 and the final result was established in March 2015. After evaluation of validity the original study protocol was retained.

Two hundred and eighty blister-packaged placebo tablets were analysed. In both test series, a value >10% of the cut-off limits for the 29 high-abrasion drugs (21 different active substances) could not be measured, the highest detected value being 8.5% of the limit. The high-abrasion drugs and cut-off values are shown in table 3.

Figure 2 Left: Analysis of the extraction supernatant of one Euthyrox 25 µg tablet to which 10 µL ultrapure water had been added before extraction. To get an overview of the expected peak, undecenylenic acid (internal standard) was not added during the extraction. The blue line is the measured absorption, the cyan blue line is the base line calculated. Right: Overlay of the chromatogram of an empty tablet (blue line) from figure 2 left with the chromatogram of one Euthyrox 25 µg tablet, to which 50 ng valproic acid had been added (red line). Neither at 3671 min (retention time of the valproate–BrMMC derivate, Peak described with Valp in the chromatogram) nor at 6197 min (retention time of the undecenylate–BrMMC derivate, Peak described with internal standard in the chromatogram) can a peak be seen in the empty tablet.

Figure 3 Representative chromatogram for one Euthyrox tablet from series 1 (left) and for one Euthyrox tablet from series 2 (right). At 3.66–3.74 min (retention time of the valproate–BrMMC derivate) no peak was detectable.

In the V-series, a value of >1.0% of the cut-off was detected in 29 samples (21% of the 140 placebos or 1.0% of the total 2940 measurements in this series, ie, 7×20 placebos ×21 substances). This affected predominantly amlodipine and folic acid with 14 and 7 values >1.0%, respectively. Apart from one sample that showed 8.5% of the cut-off value of levothyroxine and one that showed 7.2% of the cut-off of clonazepam, all values were <5.0% of the cut-off limits.

In the N-series, a value of >1.0% of the cut-off was detected in 38 samples (27% of the 140 placebos or 1.3% of the total 2940 measurements in this series, ie, 7×20 placebos ×21 substances). This affected predominantly benserazide (13×) and amlodipine (22×). Apart from a single sample that showed 6.3% of the cut-off value of benserazide, all values were <5.0% of the cut-off limits.

In the V-series, the average percentage of the 29 samples above 1.0% of the cut-off amounted to 2.4% and for the 38 samples in the N-series to 2.0%.

The results of the analyses of the 280 placebo tablets from the V-series and the N-series are available as online supplementary information.

Question 4: transferability of results to other machines

Criteria used to judge validity of result transfer are listed in table 4 and show comparable production conditions on both machines.

DISCUSSION

Main results, outcome of the cleaning validation

Our main aim was to investigate the risk of cross-contamination in our blistering machines in order to validate the cleaning procedure and to demonstrate GMP conform production. We addressed the criteria for accepting the validation in four questions.

The results showed that these validation criteria were completely fulfilled:

Table 3 List of 29 drugs classified as high-abrasion drugs with dosage form, active substances, daily doses and cut-off limits

Drug	Dosage form	Active substance	Daily dose in mg	Cut-off in µg	LOQ (50% cut-off in µg)
Urosin 300 mg	Tablets	Allopurinol	300–600	300	150
Sirdalud 2 mg	Tablets	Tizanidine	12	12	6
Folsan 5 mg	Tablets	Folic acid	5–15	5	2.5
Mysoline	Tablets	Primidone	750–1500	750	375
Triamterene cp	Tablets	Triamterene	25–100	25	12.5
		Hydrochlorothiazide	12.5–50	12.5	6.25
Solian 200 mg	Tablets	Amisulpride	400–800	400	200
Lamictal 25, 50, 100 mg	Soluble tablets	Lamotrigine	100–400	100	50
Trittico ret 75, 150 mg	Tablets	Trazodone	150–300	150	75
Neurotop retard 300, 600 mg	Tablets	Carbamazepine	800–1200	400	200
Euthyrox 50, 75, 100 µg	Tablets	Levothyroxine	0.05–0.3	0.05	0.025
Depakine 500 mg*	Film-coated tablets	Valproic acid	1400–2100	1400	700
Leponex 25, 100 mg	Tablets	Clozapine	200–450	200	100
Praxiten 15 mg	Tablets	Oxazepam	30–45	30	15
Rivotril 0.5 and 2 mg	Tablets	Clonazepam	3–6	3	1.5
Haldol 1 and 10 mg	Tablets	Haloperidol	5–40	5	2.5
Kemadrin	Tablets	Procyclidine	15–30	15	7.5
Amlodibene 5 mg	Tablets	Amlodipine	5–10	5	2.5
Akineton 2 mg	Tablets	Biperiden	3–16	3	1.5
Sormodren	Tablets	Bornaprine	6–12	6	3
Madopar† 100/25 mg	Soluble tablets	Benserazide	75–150	75	37.5
		Levodopa			

*Moderate amount of dust included because the quantity packed is particularly large and therefore risk of cross-contamination.

†Only the active substance benserazide was examined.

LOQ, limit of quantification.

Table 4 Comparison of machine characteristics reference versus second machine (second FDS or Proud); dimensions of production (first four lines in table) are based on average values for the first quarter of 2011

Machine characteristics	Reference machine	Second machine
Tablet quantity in biggest order	14 900	10 940
Drug assembly of cassette medications	233 different drugs	256 different drugs
Monthly volume of produced blisters	80 000	70 000
Monthly volume of blister-packaged tablets	156 450	88 980
Three most frequently blister-packaged drugs in biggest order	1040 Depakine 500 mg 543 Leponex 25 mg, 522 Nozinan 25 mg	525 Pantoprazol Actavis 40 mg 413 Thrombo ASS 100 mg 406 Cerebogan
Dust formation	Investigated in visual clean approach	Reduced by approximately one-third in comparison with reference FDS
Technical construction	FDS-330	Identical (second FDS) Highly similar (Proud)*
Cleanability	Basis for cleaning procedure	Identical (second FDS) Improved cleanability (Proud)†

*Proud is a technical evolution of the FDS with highly similar design including product contact surfaces like sashes, cassettes, collection and distribution devices, hoppers, etc.

†In the Proud model, sashes and divide ring drawer are more easily accessible for cleaning; the slides allow visual control of cleaning. The Proud model incorporates a residue tray to catch the dust arising from upper machine parts.

1. The machine was visibly clean after cleaning.
2. No contamination above the dose criterion was detectable in the two WCSs. Contamination values—if at all detectable—being far below the cut-off limits, even before servicing, in maximally soiled condition of the machine, definitely rule out pharmacologically relevant cross-contamination and ensure patient safety.
3. Characteristics of construction, production dimensions and cleanability render the results valid also for our second machine.

Therefore, the cleaning validation was successfully completed.

A 'before and after' cleaning effect clearly showed in visual clean, but could not be established based on the analytical data due to no measurable contamination (WCS A) independent of the cleaning status and extremely low values already before cleaning (WCS B).

Regarding the investigation of cross-contamination in blister machines, Huat *et al*¹⁵ found similar results in terms of residues below the dose criterion.

Background

Blister packaging is demanding in the context of cleaning validation, for it repackages a large number of potentially dust-producing drugs in one batch. Preventative methods like segregated areas or separation in time²² common in pharmaceutical production are not applicable. Testing for residues requires a well-considered definition, which drugs should be analysed from this large pool of simultaneously handled substances. The described validation protocol shows our approach to overcome these difficulties by combining visual clean with two different WCSs.

To allow realistic inspection of possible contamination, all investigations were designed and carried out adopting real production conditions: Tablet quantities used in WCS A corresponded to the biggest weekly order. Placebo tablets in WCS B were directly blister-packaged in the course of such an order. Also visual inspections of the different machine parts were carried out concurrently to normal production.

Our approaches conform to the GMP requirement that validation for manual cleaning should be based on worst case situations.¹²

Rationale and limitations of visual clean

Visual control confirmed efficiency of cleaning and validity of the cleaning procedure, since only reasonably little soiling was to be seen before the intended cleaning intervals—larger aggregation would indicate too long intervals—and no soiling was observable after cleaning. Coarser soiling, like drug fragments of broken tablets, was only sporadically seen and is not critical in the sense of cross-contamination, since it is not layered onto other tablets.

Swabbing tests in the visual clean assessment were intended only for better visualisation of dust not for analytical investigation of the swabbing material. Therefore, an obvious limitation is that the results are to a certain point operator-dependent. Besides, not all contamination might be visible. Also the passing of time—not avoidable with up to quarterly inspection intervals—complicated consistency of the assessment. We aimed to establish highest possible standardisation and validity of the visual tests by restricting to one operator, one special wiping cloth and a detailed protocol on machine parts, modes and dates to perform the tests.

Visual tests of machine cleanliness were only one part of the validation process and were confirmed by other examinations, as required in GMP.

These considerations support the validity of the results.

Rationale and limitations of WCS A

No valproate was detectable on any of the Euthyrox tablets. This applies notwithstanding how the blister-packaging procedure in series 1 and series 2 differed in respect to cleaning status of the machine. With a limit of detection of the analytical method well under the LOQ of 10 ng, the actual contamination was definitely below the required limit of 1:1000 and also below 1:10 000. Even if a patient took 12 Euthyrox 25 µg tablets per day, this person would receive less than the cut-off of 0.14 mg valproic acid. Contamination, which could put patients at risk, could with all probability be excluded.

The contamination limit of 1/1000 of the daily dose of a drug, also applied in WCS B, is widely accepted for assessment of residues. According to the International Conference on Harmonisation, residue limits should be based on the minimum known pharmacological activity of the active pharmaceutical ingredient and Eudralex Volume 4 Annex 15 states that limits

for the carry-over of product residues should be based on a toxicological evaluation.^{12–23} The dose criterion meets these requirements of GMP and Pharmaceutical Inspection Convention (PIC) being rational from a pharmacological point of view: Assuming the daily dose targets 90% of the maximum achievable therapeutic effect, then, according to the mass action law, a thousandth of the dose will cause <1% of this effect. An effect which represents 1% of the maximum effect is clinically not verifiable. Furthermore, this assumption is based on a dose–effect curve the way it appears from the point of view of receptor occupation. Actually, the dose–effect curve in clinical practice is based on the distribution of individual sensitivity. The dose–effect curve is therefore much steeper than may be expected from the mass action law. In other words, with a dose reduction to 1/1000 there is clinically no relevant effect, side effect or interaction to be assumed and a large safety margin is built in so that even with substances with a long half-life, sensitivities of individuals to specific chemicals or patients with limited elimination capacity (eg, kidney function disorder, polymorphism in the hepatic enzymes), a risk to patients treated can be excluded.

The choice of Euthyrox in WCS A is rational: it is most vulnerable to contamination: as a simply pressed tablet, with a structured surface (including cross-scoring and raised lettering), it picks up dust easily. Euthyrox 25 µg tablets are packed in small numbers per order and contain low active substance. Contamination is most critical for such tablets.

The choice of Depakine needs further explanation: Depakine, as film-coated tablet, is from the technological point of view not very dust-forming, which also showed in our swabbing tests. But Depakine is by far the most frequently repacked drug in the machine with an average quantity over 1000 in the biggest order—twice as much as the next in row, Leponex 25 mg. It shows the highest value in our setting multiplying tablet quantity with active substance content per tablet. Considering these facts, possible cross-contamination from Depakine had to be included in the analyses for the cleaning validation. Therefore, WCS A was set up with Depakine as a major component; WCS B also included Depakine for the explained reasons.

Rationale and limitations of WCS B

Testing for residues of all medications in the machine is not possible due to their large number. A more practical way, followed in WCS B, is to identify drugs most critical in terms of contamination, that is, highly abrasive drugs. These were found via systematic observation of dust production of repackaged medications. Therefore, WCS B rests upon visual assessment, whose limiting aspects are discussed before. Abrasion classification of the cassette drugs, however, was strengthened by technological considerations and by years-long experience with the cassette medications, which confirmed validity of the results.

The classification is of course specific for our setting; it reflects the dust formation potential of the drugs only in combination with the actual consumption.

In all placebo tablets, detected contaminations of the high-abrasion drugs did not even reach 10% of the contamination limits, most values were under 1/20 or below 1/100 of the established limits. The validation was clearly fulfilled but quantitative interpretability of the obtained data is limited, since they lie well below the LOQ. Contamination seems comparable in maximal and minimal clean status of the machine. This reflects that establishing a difference in contamination levels is difficult and has limited significance when extremely low values, like in

our case, are involved, where roughly 80% of the samples do not even reach 1% of the examined limits.

A strength of WCS B lies in the fact that it takes into account that contamination from one active substance does not solely come from one drug but from several drug potencies; For example Neurotop retard 300 and 600 mg tablets are both classified as high-abrasion drugs. In this approach, the total carbamazepine contamination on the placebo tablets is determined irrelevant of its source.

The placebo tablets used for the study were by all means suitable for this test: (a) As simply pressed tablets with a structured surface, the placebos were especially at risk of contamination. (b) We filled them in one of the upper cassettes of the blister machine. So they took as long a route through the machine as possible—increasing the chances to absorb dust from other tablets.

Designed in autumn 2011, the delayed start of WCS B in summer 2014 could be argued. However, in a critical comparison it was established beforehand, that the prerequisites for the machines had remained almost unchanged since 2011 (type and quantities of repacked medications, highly dust-producing drugs, workload on the machine, order characteristics, etc), so the original scenario was retained. This intense evaluation, which showed highly stable production conditions, confirms the validity of the results despite the delayed execution of the protocol and justifies sticking to the initial study design.

Rationale and limitations of transferring the results to other machines

PIP guidelines⁹ support utilisation of representative processes and worst case approaches. Therefore, we intended to transfer the study results from one reference machine, which holds a wide and adequate selection of drugs and represents the ‘riskiest’ production conditions, to the second machine. The latter supplies smaller institutions (nursing homes), shows less visible dust formation and operates smaller batch sizes and volumes of the individual repacked drugs, which means reduced risk: even a highly dust-forming tablet cannot generate high amounts of abrasion if used only in small quantities. *Sine qua non* for data transferability was identical machine construction, met in the case of the second FDS or highly similar technical design accomplished by the Proud model (especially of product contact surfaces like sashes, cassettes, hoppers etc). Additionally, the Proud model is easier to clean and incorporates a residue tray to catch the dust from upper machine parts. Based on these facts, we judged the results established from studies on the reference machine representative.

Significance for other production sites

In the course of the GMP audits, our cleaning validation was inspected and affirmed by the Austrian authorities in 2011 (analytical part of WCS B still pending) and in 2015. So it might be used as a reference for other production sites (eg, hospital pharmacies with focus on neuropsychiatric drugs). Transferability of the results is of course limited to settings comparable in terms of type of blistering machines and cleaning standard, drug composition, quantities repackaged, batch sizes, volume of production, etc. The methods described might also give ideas to set up a cleaning validation for a blister packaging machine in sites with diverging characteristics.

Conclusion

The study contributes evidence that blister repackaging is safe in terms of drug cross-contamination provided that a valid cleaning

standard is established that meets the requirements of one's particular production setting.

Visual cleanliness was achieved. The analytical results confirmed the effectiveness of machine cleaning preventing cross-contamination from repacked drugs. Residues were either not even measurable or at extremely low values so that pharmacological effects could be ruled out at any time. The results are valid for the whole site. For similar production sites, the study might serve as a reference.

In any case, establishment and validation of a cleaning procedure must always go along with risk minimisation and quality assurance tools: intensive, repeated staff training, appropriate documentation and continuous monitoring of cleaning activities, proper error culture, continuous improvement process, change management and, where necessary, revalidation.

Key messages

What is already known on this subject?

- Literature is rare on cross-contamination in blister machines.
- Huat *et al* found contaminations of copackaged drugs below the maximally allowable limits on blister-packaged tablets.
- Implementing Good Manufacturing Practice in our blister setting required the validation of our blister machine cleaning procedure.

What this study adds?

- Blister packaging and machine cleaning are for the first time extensively validated: visual clean, risk assessment, analytical measurements (high performance liquid chromatography, mass spectrometry), dose criterion for pharmacological relevance of detected contamination.
- The results confirmed product quality and patient safety and may serve as reference for similar settings.

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Contributors All authors made a substantial contribution to the conception of the survey described in the article. The cleaning validation was planned, conducted, interpreted and reported by TMS-S, quality manager of our blister setting. GG, qualified person, supervised the process and contributed to the study design. AT, responsible pharmacist for blister production, was involved in preparing the manuscript (data presentation, statistical evaluation, generation of Figures and Tables, etc). Doz. Thomas Müller, central laboratory, hospital Barmherzige Brüder Linz, critically reviewed the manuscript. Professor Michael Freissmuth, Institute of Pharmacology, University of Vienna, and Professor Rainer Schmid, Clinical Department of Laboratory Medicine, Medical University of Vienna, carried out the analytical parts of the study (mentioned in the Acknowledgements).

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REFERENCES

- 1 Bundesgesetz vom 2. März 1983 über die Herstellung und das Inverkehrbringen von Arzneimitteln (Arzneimittelgesetz—AMG), AMG, 1983.
- 2 Bardage C, Ekedahl A, Ring L. Health care professionals' perspectives on automated multi-dose drug dispensing. *Pharm Pract (Granada)* 2014;12:470.
- 3 Bell JS, Johnell K, Wimmer BC, *et al*. Multidose drug dispensing and optimising drug use in older people. *Age Aging* 2013;42:556–8.
- 4 Kwint HF, Stolk G, Faber A, *et al*. Medication adherence and knowledge of older patients with and without multidose drug dispensing. *Age Aging* 2013;42:620–6.
- 5 Murray MD, Shojania KG. *Making health care safer: a critical analysis of patient safety practices*. Chapter 10: Unit-Dose Drug Distribution Systems. AHRQ Publication, 2001.
- 6 Sinnemäki J, Sihvo S, Isojärvi J, *et al*. Automated dose dispensing service for primary healthcare patients: a systematic review. *Syst Rev* 2013;2:1.
- 7 European Commission. Eudralex Vol 4: EU guidelines to good manufacturing practice medicinal products for human and veterinary use. In: Directorate-General HaC, ed. Brussels: European Commission, 2010. http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm
- 8 Österreichische Agentur für Gesundheit und Ernährungssicherheit. <http://www.ages.at/startseite/>
- 9 PIC/S Pharmaceutical Inspection Convention / Pharmaceutical Inspection Co-operation Scheme. Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-sterile Process Validation, Cleaning Validation, PI 006-3 www.picscheme.org, 2007.
- 10 Baxter. Utrecht: Baxter Nederland B.V. <http://www.baxter.nl>
- 11 Academy E. Justification of Limits for Cleaning Validation in the Manufacture of Active Pharmaceutical Ingredients, 2007. http://www.gmp-compliance.org/eca_news_928.html (26 Oct 2015).
- 12 Commission E. Annex 15 Qualification and Validation, Eudralex Vol 4: EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, <http://ec.europa.eu/health/files/eudralex/vol-4/>, (2015).
- 13 LeBlanc DA. "Visually clean" as a sole acceptance criterion for cleaning validation protocols. *PDA J Pharm Sci Technol* 2002;56:31–6.
- 14 Aide-mémoire: Maschinelles patientenindividuelles Verblistern von Arzneimitteln. In: AATB UAadVvAdA, ed. Bonn: Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten, 2010. https://www.zlg.de/index.php?elD=tx_nawsecuredl&u=0&file=fileadmin/downloads/AM/QS/07120201.pdf&hash=b8a0a5630b0471f267a6600fe3b682c6106eb9df
- 15 Huat TC, Hong GL, Seng WT. Drug Cross-Contamination of Barcode Unit Dose Repackager in a Tertiary Academic Medical Centre. *J Pharm Pract Res* 2014;44:17–21.
- 16 Schülke&Mayr. Norderstedt: Schülke & Mayr GmbH, 2015. <http://www.schuelke.com/at/de/default/48908.php?q=mikrozid+af+liquid>
- 17 Floorstar. Floorstar GmbH (4.11.2015). <http://www.floorstar.de/produkte/tuecher/microfaser/>
- 18 Fagron. Fagron GmbH & Co KG (4.11.2015). <https://shop.fagron.de/de-de/product/700099/placebo-tabletten-2c-oval.aspx>
- 19 Paltala I, Heinämäki J, Honkanen O, *et al*. Towards more reliable automated multi-dose dispensing: retrospective follow-up study on medication dose errors and product defects. *Durg Dev Ind Pharm* 2013;39:489–98.
- 20 Voigt R. *Pharmazeutische technologie*. 11 edn. Deutscher Apothekerverlag, 2010.
- 21 Zimmermann I. *Pharmazeutische Technologie: Industrielle Herstellung und Entwicklung von Arzneimitteln*. Berlin, Heidelberg, New York, Barcelona, Budapest, Hong Kong, London, Mailand, Paris, Santa Clara, Singapore, Tokyo: Springer, 1998.
- 22 PIC/S Pharmaceutical Inspection Convention / Pharmaceutical Inspection Co-operation Scheme. Guide to Good Manufacturing Practice for Medicinal Products Part 1, PE-009-12 www.picscheme.org, (2014).
- 23 ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, www.ich.org, (2000).