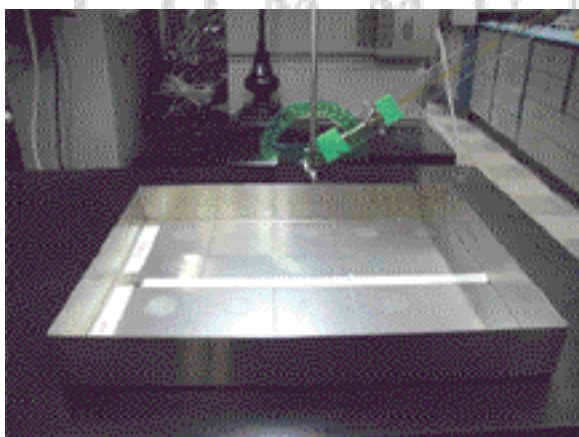


# Visible-Residue Limit for Cleaning Validation and its Potential Application in a Pharmaceutical Research Facility

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Evaluations have shown that, in most cases, visual observations are sensitive enough to verify equipment cleanliness. An experiment was conducted to explore the possibility of using a visible-residue limit as an acceptable cleaning limit in a pharmaceutical research facility, including an evaluation of the limits and subjectivity of “visually clean” equipment.

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Visual inspections for equipment cleanliness have always been conducted in pharmaceutical facilities operating according to good manufacturing practices. Before validated cleaning programs existed, formulators visually inspected equipment before commencing formulation work (1). Since formalized cleaning validation programs were introduced, however, analytical testing has been the preferred method for verifying and validating acceptable-residue limit (ARLs) for equipment cleanliness. Because analytical test methods are quantitative and validated, the results provide solid documentation of the equipment cleaning process. Analytical testing removes much, if not all, of the subjectivity of residue determination.

Visual inspections for cleanliness have continued to be performed, however, in conjunction with the analytical methods. A visual inspection is conducted and visible cleanliness is confirmed before any sample is taken for chemical analysis (2). Visual inspection also is required before any formulation work is begun.

The use of only a visual assessment to determine equipment cleanliness was proposed in 1989 by Mendenhall (3). He found that visible-cleanliness criteria were more rigid than quantitative calculations and clearly adequate. The Food and Drug Administration, however, in its 1993 “Guide to Inspection of Validation of Cleaning Processes,” limited the potential acceptability of a visually clean criterion to use between lots of the same product (4). The adequacy of visible-residue limits (VRLs) has continued to be a topic of discussion since then. A recent article by LeBlanc again raised the question of whether a visible limit could be justified as the sole acceptance criterion for equipment cleanliness (5).

*Visible cleanliness* is the absence of any visible residue after cleaning. Although this definition seems straightforward, various factors influence the determinations made using this method. The most obvious variable is the observer. The outcome of a visual inspection depends not only on the observer’s visual accuracy, but also on what the observer is trained to see. Lighting levels in inspection areas, shadows caused by equipment, and the observer’s viewing angle and distance from the equipment surface also influence what is seen. In addition, the chemical composition of the cleaning solvents can change the appearance of the residue. Finally, the individual components

**Table I: Light intensities in the manufacturing pilot-plant suite.**

Room	Lx	Room	Lx
2420A	540	2736	1090
2420B	600	2737	940
2420C	630	2738	520
2702A	670	2740	600
2702B	650	2742	1050
2702C	670	2744	840
2720	680	2746	1060
2722	870	2747	1120
2723	850	2748	870
2725	920	2749	1400
2726	1230	2750	700
2727	640	2751	640
2729A	1170	2752	870
2729B	770	2753	1130
2730	700	2754	1170
2731	770	2755	740
2732	1190	2756	1240
2733	1170	2757	1170
2734	1080	2758	1240
2735	1240	2759	1350

of a given formulation affect the overall VRL. Fourman and Muller determined a visible limit of ~100 µg per 2 × 2 in. swab area or approximately 4 µg/cm<sup>2</sup> (6). Jenkins and Vanderwiel observed various residues as low as 1.0 µg/cm<sup>2</sup> with the aid of a light source (7).

The ARL for drug residue is often determined on a health-based or adulteration-based criterion (2, 7, 8). The limit used is the lower of the two limits. A health-based limit is generated from toxicity data, which can be expressed as allowable daily intake (ADI). Based on the author's experience, if the ADI is <0.1 mg/day, the health-based limit will be the lower of the two limits. The adulteration limit, on the other hand, will generally be lower for substances with ADI values >0.1 mg/day. The health-based limit is calculated using the ADI and the param-

eters of the manufacturing equipment (2). For the adulteration limit, a constant level of 10 ppm or 100 µg/swab is often used in the industry.

If the VRL could be quantitatively established and shown to be lower than the ARL, then it might be reasonable to use a visible-residue criterion for cleaning validation. The ARL is logically established, through analytical testing, for the most potent component of a formulation, which is usually the active pharmaceutical ingredient (API). To consider a nonselective, visually clean criterion, one would have to consider the individual VRLs of both the excipients and APIs in the formulation.

For this study, the VRLs were determined for various APIs, commonly used excipients, and drug formulations. The residue limits for the formulations were then compared with the limits for the individual formulation components. The VRLs for the detergents used to clean the equipment also were assessed, because the detergents are part of the overall manufacturing process.

### Visible-residue parameters

Because determining a VRL is highly subjective, the variables associated with studying visible residues were defined and then experimental parameters for the study were established. The parameters considered were surface material, solvent effects, light intensity, and observer distance, angle, and subjectivity.

Stainless steel was an obvious choice for surface material because more than 95% of manufacturing equipment surfaces are stainless steel. For this study, representative stainless steel coupons were used for spotting purposes in the laboratory setting. If VRLs were used in an operating facility, additional materials such as PTFE, rubber, or plastics would have to be tested.

The lighting conditions in the manufacturing pilot plant differed from room to room. The light intensity was measured in each room of the pilot plant and the wash area to determine the range of light intensity. For consistency, the light measurement was taken in the center of each room at ~4 ft from the floor. Table I lists the range of light intensities in the various rooms in the pilot-plant suite. The light intensity ranged from 520 to 1400 lx. To account for this variation as well as for shad-

**Table II: Observer variability of visual cleanliness of carnauba wax versus light intensity.\***

Drug/spot µg/cm <sup>2</sup>	Detection of spots by observers A–D																			
	1400 lx				1000 lx				800 lx				600 lx				400 lx			
	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
22.7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
14.5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6.34	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3.99	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2.10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
1.92	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N
0.907	Y	N	N	N	Y	Y	N	N	Y	N	N	N	Y	N	N	N	Y	N	N	N
<0.907	N	N	N	N	Y	N	N	N	Y	N	N	N	N	N	N	N	Y	N	N	N
0.000	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

\*Compound is carnauba wax in 1:1 acetonitrile:water. All spots were observed under fluorescent light. Y indicates spot was observed. N indicates no spot was observed.

**Table III: Observer variability of visual cleanliness of apreitant versus light intensity.\***

Drug/spot $\mu\text{g}/\text{cm}^2$	Detection of spots by observers A–D																			
	1400 lx				1000 lx				800 lx				600 lx				400 lx			
	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
74.4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
40.1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
14.2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12.0	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7.44	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5.90	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2.98	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
1.45	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
0.00	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

\*Compound is apreitant in 1:1 acetonitrile:water. All spots were observed under fluorescent light. Y indicates spot was observed. N indicates no spot was observed.

ows and different locations within a room, the visible-residue study was conducted between 400 and 1400 lx using a light source directly above the sample. A fluorescent light provided the same type of light that is used in the pilot plant. A plastic cover with various degrees of shading was placed over the bulb and was rotated to adjust and control light intensity. A light meter was used to set and verify the various light intensity levels.

To minimize observer subjectivity, four subjects viewed all of the samples. The angle and distance of the observer relative to the samples were tested next. A distance of 6–18 in. from the equipment surface and a viewing angle of 0–90° were considered as practical viewing parameters. The first set of spots was prepared and viewed from various distances and angles. The distance did not have a significant effect, however, so a comfortable viewing distance of 12 in. was chosen. The viewing angle, on the other hand, turned out to be a critical variable. A 90° angle (looking at the spots from directly overhead) was not the optimal angle, because spots were not as easily seen. Having the observer and the light source at the same angle significantly reduced the visible reflectance from the residue. In addition, increased reflectance interference occurred from the surrounding surfaces. Decreasing the viewing angle made the spots more visible to the observer because of the reflectance of light off the residue. A viewing angle of 30° was chosen, although smaller angles occasionally provided more reflectance. A 30° angle provided the shallowest practical viewing angle, taking into consideration the surface locations where residues are most likely to be seen in manufacturing equipment (*i. e.*, corners and joints).

Finally, solubility and solvent effects were considered. A list of solubilities for each excipient and API was compiled. Initially, various solvents were used with the APIs. That resulted in a wide range of residue spot areas (3–32 cm<sup>2</sup>), however, which made it problematic to determine a consistent amount per unit area ( $\mu\text{g}/\text{cm}^2$ ) for each material. Also, several excipients were only soluble in extremely harsh solvents, and buffers, acids, and bases were not desirable because they would leave their own residues on the surface. The investigators decided to use a solvent of 1:1 acetonitrile:water for all APIs and excipients. The solvent left

no residue and provided adequate solubility for a majority of the substances tested, and the spot-area range (5–15 cm<sup>2</sup>) was much tighter. If solubility was not achieved, the material was suspended and samples were spotted immediately using the suspension.

The solvent also had an effect on the spots themselves. The majority of the residues were white crystalline spots. Several materials left grey spots resembling water stains. The dissolution and subsequent recrystallization of the material most likely generated amorphous residues. In all of the trials, the solvent was spotted to confirm that it did not leave a residue. An unspotted stainless steel coupon was used as a control for each study.

### Experiment

Samples were prepared by dissolving or dispersing 25 mg of material into 50 mL of solvent, resulting in a 0.5 mg/mL or 500  $\mu\text{g}/\text{mL}$  sample. Various volumes of the sample were spotted on to the stainless steel coupons along with a complementary volume of solvent so that the total volume spotted was constant. Eight residues were spotted for each sample along with a solvent blank. The resulting range of spots was between 5 and 300  $\mu\text{g}/\text{mL}$ .

The spots were dried under a stream of nitrogen to aid in drying and to prevent potential oxidation of the material, because drying spots under a stream of air can oxidize some materials that are not easily oxidized. Even though the same volume of sample or solvent was spotted, different dried residue areas appeared as the liquid samples spread over the coupon. That variation in spot size resulted from differences in surface tension of the samples and from passing nitrogen over the samples during drying. The areas of the dried spots were measured to determine the amount per unit area ( $\mu\text{g}/\text{cm}^2$ ) for each spot of material. The range of areas for the spots observed in the trials was 0.1–106  $\mu\text{g}/\text{cm}^2$  (see Figure 1).

The spots were viewed under controlled conditions. The light source was maintained in a stationary position directly above the samples. The observers were oriented such that they viewed the spots from the same three-dimensional location each time. Each observer wore a white lab coat to minimize variations caused by individual clothing colors. The observers viewed the

**Table IV: Visible-residue limits of commonly used excipients versus light intensity.**

Excipient*	Visible limit ( $\mu\text{g}/\text{cm}^2$ ) at specified illuminance				
	400 lx	600 lx	800 lx	1000 lx	1400 lx
Ascorbic acid	<0.878	<0.878	<0.878	<0.878	<0.878
Calcium phosphate, dibasic anhydrous	<0.463	<0.463	<0.463	<0.463	<0.463
Calcium phosphate, dibasic dihydrous	1.31	1.31	3.12	1.31	1.31
Cellulose, microcrystalline	1.11	1.11	2.42	2.42	1.11
Croscarmellose sodium	3.09	3.09	3.09	3.09	3.09
Ferric oxide, red	1.55	1.55	1.55	1.55	1.55
Ferric oxide, yellow	<0.584	<0.584	<0.584	<0.584	<0.584
Hydroxypropyl cellulose	<0.490	<0.490	<0.490	<0.490	<0.490
Lactose anhydrous	<0.684	<0.684	<0.684	<0.684	<0.684
Lactose monohydrate	<0.597	<0.597	<0.597	<0.597	<0.597
Magnesium stearate	<0.469	<0.469	<0.469	<0.469	<0.469
Mannitol	<0.673	<0.673	<0.673	<0.673	<0.673
Poloxamer 188	0.808	<0.362	<0.362	<0.362	<0.362
Poloxamer 407	<0.366	<0.366	<0.366	<0.366	<0.366
Propyl gallate	<0.681	<0.681	<0.681	<0.681	<0.681
Silicon dioxide, colloidal	10.9	10.9	10.9	10.9	15.3
Sodium lauryl sulfate	<0.963	<0.963	<0.963	<0.963	<0.963
Sodium starch glycolate	<0.403	<0.403	<0.403	<0.403	<0.403
Sodium stearyl fumarate	2.12	1.52	1.52	0.511	0.511
Starch, partially pregelatinized corn	10.2	10.2	10.2	10.2	10.2
Sucrose	<0.61	<0.61	<0.61	<0.61	<0.61
Titanium dioxide	1.92	1.92	1.92	2.10	2.10
Wax, carnauba	5.15	5.15	5.15	5.15	5.15

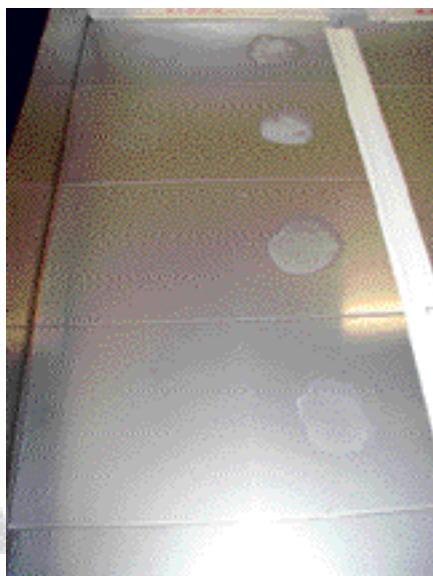
\* The solvent used for all excipients was 1:1 ACN:water.

coupons separately so as not to influence the responses of the other participants. The coupons were positioned for viewing and the light intensity was measured from the same spot on the bench top each time (see Figure 2).

## Results and discussion

VRLs were established for 23 commonly used excipients and 22 APIs. Each visible limit was designated as the concentration at which all observers positively identified a visible residue. The actual amount of material spotted (in  $\mu\text{g}/\text{cm}^2$ ) was a result of the amount of excipient or API weighed for the sample, the volume of solution or suspension spotted on the coupon, the subsequent area of the liquid on the coupon, and the resulting residue area. The four observers viewed the spots and indicated whether or not they saw any visible residue. Examples of the results of one excipient and one API are shown in Tables II and III, respectively.

The detergents used to clean the equipment at this facility

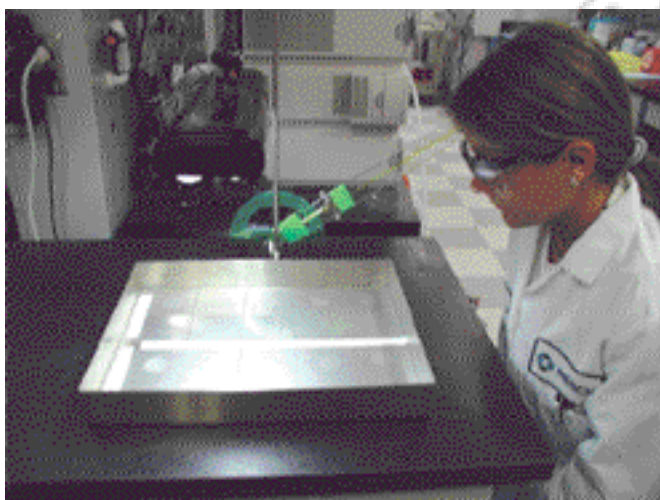


**Figure 1: Representative residues on stainless steel.**

were the first substances tested. It was necessary to confirm that the detergent VRLs were low enough to not interfere with visible residue determinations of formulations produced in the pilot plant. A base detergent and a neutral detergent are used during different stages of the cleaning process. The VRLs of the base and neutral detergents were  $<0.37$  and  $<0.56 \mu\text{g}/\text{cm}^2$ , respectively. Because these limits were sufficiently lower than the adulteration limit of  $4 \mu\text{g}/\text{cm}^2$ , the testing of lower residue levels was not considered necessary.

A list of commonly used excipients was compiled for evaluation. Most of the common fillers were tested because filler is typically the main ingredient in a formulation after the API. In addition, representative samples of lubricants, binders, disintegrants, antioxidants, and colorants were tested. Table IV lists the excipients

tested. The data showed that the VRL ranged from  $<0.366$  to  $15.3 \mu\text{g}/\text{cm}^2$  across the light intensities monitored in the study. The highest VRL obtained across the light intensities was con-



**Figure 2:** Observer examining stainless steel coupons for residues.

considered the VRL because this was the most conservative approach. Fourteen of the excipients had limits  $<1.0 \mu\text{g}/\text{cm}^2$ , two had limits between 1 and  $2 \mu\text{g}/\text{cm}^2$ , five were between 2 and  $4 \mu\text{g}/\text{cm}^2$ , and three were  $>4 \mu\text{g}/\text{cm}^2$ . Twenty-one of the 23 excipients tested were at or below the adulteration limit of  $4 \mu\text{g}/\text{cm}^2$ . This would indicate that formulations containing these excipients might be candidates for a visual cleaning inspection.

Light intensity was the only study condition that was varied. When Fouman and Mullen determined a visible limit at approximately  $4 \mu\text{g}/\text{cm}^2$ , they did not address the light intensity and individual residues (6). With light source, however, Jenkins and Vanderwiel en observed various residues as low as  $1.0 \mu\text{g}/\text{cm}^2$  (7). One could logically expect the VRL to decrease with increasing light intensity. The excipient results obtained in this study, however, were significantly different from that expectation. Of the 23 excipients tested, 17 of the limits were the same regardless of the light intensity (see Table IV). Only 2 limits decreased with an increase in light intensity, and two of the limits actually increased with an increase in light intensity.

Three of the limits increased as light intensity increased and then subsequently decreased as the light intensity was increased further. It was hypothesized that the change in VRL was caused by the interaction of the precipitating excipient, the evaporating solvent, and the stainless steel plate. Although there were changes in the detected VRL, the changes were minor. No excipient went from below to above the  $4 \mu\text{g}/\text{cm}^2$  limit or *vice versa*.

Twenty-two APIs also were evaluated for their VRLs (see Table V). A combination of marketed and developmental compounds was tested. The marketed products contained APIs that were tested separately in this study. Testing marketed products provided a more extensive database for the study. The data showed that the VRLs ranged from 0.40 to  $6.25 \mu\text{g}/\text{cm}^2$  across the light intensities monitored in the study. The highest VRL obtained across the light intensities was again considered the VRL. Seven of the APIs had limits  $<1.0 \mu\text{g}/\text{cm}^2$ , 7 had limits between 1 and  $2 \mu\text{g}/\text{cm}^2$ , 3 were between 2 and  $4 \mu\text{g}/\text{cm}^2$  and 5 were  $>4 \mu\text{g}/\text{cm}^2$ . Seventeen of the 22 APIs tested were at or below the adulteration

**Table V: Visible residue limits of formulations versus light intensity.**

API <sup>†</sup>	Visible-residue limit ( $\mu\text{g}/\text{cm}^2$ ) at specified illuminance				
	400 lx	600 lx	800 lx	1000 lx	1400 lx
Losartan potassium (Cozaar <sup>**</sup> )	<2.68	<2.68	<2.68	<2.68	<2.68
Indinavir sulfate (Crixivan <sup>*</sup> )	<1.38	<1.38	<1.38	<1.38	<1.38
Aprepitant (Emend <sup>*</sup> )	–	1.45	1.45	1.45	1.45
Cyclobenzaprine HCL (Flexeril <sup>*</sup> )	<1.89	<1.89	<1.89	<1.89	<1.89
Alendronate sodium (Fosamax <sup>*</sup> )	0.495	0.495	0.495	0.495	0.239
Rizatriptan benzoate (Maxalt <sup>*</sup> )	<0.873	<0.873	<0.873	<0.873	<0.873
Famotidine (Pepcid <sup>*</sup> )	<1.46	<1.46	<1.46	<1.46	<1.46
Finasteride (Proscar <sup>*</sup> )	<2.72	<2.72	<2.72	<2.72	<2.72
Montelukast sodium (Singulair <sup>*</sup> )	<1.47	<1.47	<1.47	<1.47	<1.47
Enalapril maleate (Vasotec <sup>*</sup> )	<0.65	<0.65	<0.65	<0.65	<0.65
Rofecoxib (Vioxx <sup>*</sup> )	5.64	0.871	0.871	0.871	0.871
Simvastatin (Zocor <sup>*</sup> )	0.485	0.485	0.400	0.485	0.485
Compound A	0.552	0.552	0.552	0.552	0.552
Compound B	<0.591	<0.591	<0.591	<0.591	<0.591
Compound C	0.666	0.666	0.666	0.666	0.666
Compound D	5.59	1.61	1.61	1.61	1.61
Compound E	5.85	1.85	1.85	1.85	1.85
Compound G	–	6.25	6.25	6.25	6.25
Compound H	1.75	1.75	1.75	1.75	1.10
Compound I	3.01	3.01	3.01	3.01	3.01
Compound J	–	5.43	0.930	0.930	0.930
Compound K	1.97	1.97	1.97	1.97	1.97

\* Registered trademark of Merck & Co. in certain countries.

\*\* Registered trademark of E.I. du Pont de Nemours and Company (Wilmington, DE).

† The solvent used for all compounds was 1:1 acetonitrile:water, except for Simvastatin and Compound K, for which 4:1 acetonitrile:water was used, and Compound D, for which 4:1 methanol:water was used.

**Table VI: Visible-residue limits ( $\mu\text{g}/\text{cm}^2$ ) of marketed formulations and formulation components.**

	<b>Ingredient</b>	<b>VRL</b>		<b>Ingredient</b>	<b>VRL</b>
<b>Cozaar</b>	formulation	<0.505	<b>Proscar</b>	formulation	<0.44
Losartan potassium	API	<2.68	Finasteride	API	<2.72
Microcrystalline cellulose	excipient	2.42	Microcrystalline cellulose	excipient	2.42
Lactose hydrous	excipient	<0.597	Lactose hydrous	excipient	<0.597
Starch, pregelatinized	excipient	10.2	Starch, pregelatinized	excipient	10.2
Magnesium stearate	excipient	<0.469	Magnesium stearate	excipient	<0.469
<b>Crixivan</b>	formulation	<1.1	Sodium starch glycolate	excipient	<0.403
Indinavir sulfate	API	<1.38	Ferric oxide, yellow	dye	<0.584
Lactose anhydrous	excipient	<0.684	<b>Singulair</b>	formulation	<0.4
Magnesium stearate	excipient	<0.469	Montelukast sodium	API	<1.47
<b>Emend</b>	formulation	<0.34	Hydroxypropyl cellulose	excipient	<0.490
Aprepitant	API	1.45	Microcrystalline cellulose	excipient	2.42
Microcrystalline cellulose	excipient	2.42	Lactose hydrous	excipient	<0.597
Sodium lauryl sulfate	excipient	<0.963	Croscarmellose sodium	excipient	3.09
Hydroxypropyl cellulose	excipient	<0.490	Magnesium stearate	excipient	<0.469
Sucrose	excipient	<0.61	Titanium dioxide	excipient	2.10
<b>Flexeril</b>	formulation	<0.82	Carnauba wax	excipient	5.15
Cyclobenzaprine HCl	API	<1.89	Ferric oxide, red	dye	1.55
Lactose hydrous	excipient	<0.597	<b>Vasotec</b>	formulation	<1.4
Pregelatinized starch	excipient	10.2	Enalapril maleate	API	<0.65
Starch, corn	excipient	10.2	Lactose hydrous	excipient	<0.597
Magnesium stearate	excipient	<0.469	Starch, pregelatinized	excipient	10.2
Ferric oxide, yellow	dye	<0.584	Magnesium stearate	excipient	<0.469
<b>Fosamax</b>	formulation	<0.46	Starch	excipient	10.2
Alendronate sodium	API	0.495	Ferric oxide, red	dye	1.55
Microcrystalline cellulose	excipient	2.42	Ferric oxide, yellow	dye	<0.584
Lactose anhydrous	excipient	<0.684	<b>Vioxx</b>	formulation	<0.59
Croscarmellose sodium	excipient	3.09	Rofecoxib	API	5.64
Magnesium stearate	excipient	<0.469	Microcrystalline cellulose	excipient	2.42
<b>Maxalt</b>	formulation	<0.61	Lactose monohydrate	excipient	<0.597
Rizatriptan benzoate	API	<0.873	Hydroxypropyl cellulose	excipient	<0.490
Microcrystalline cellulose	excipient	2.42	Croscarmellose sodium	excipient	3.09
Lactose hydrous	excipient	<0.597	Magnesium stearate	excipient	<0.469
Starch, pregelatinized	excipient	10.2	Ferric oxide, yellow	dye	<0.584
Ferric oxide, red	dye	1.55	<b>Zocor</b>	formulation	<0.57
<b>Pepcid</b>	formulation	<0.33	Simvastatin	API	0.485
Famotidine	API	<1.46	Cellulose	excipient	2.42
Microcrystalline cellulose	excipient	2.42	Hydroxypropyl cellulose	excipient	<0.490
Hydroxypropyl cellulose	excipient	<0.490	Hydrous lactose	excipient	<0.597
Magnesium stearate	excipient	<0.469	Magnesium stearate	excipient	<0.469
Titanium dioxide	excipient	2.10	Titanium dioxide	excipient	2.10
Ferric oxide, red	dye	1.55	Ascorbic acid	excipient	<0.878
			Ferric oxide, red	dye	1.55
			Ferric oxide, yellow	dye	<0.584

limit of  $4 \mu\text{g}/\text{cm}^2$ . However, if the two lowest light intensities were excluded, the VRLs for 4 of the 5 APIs with VRLs  $>4 \mu\text{g}/\text{cm}^2$  would fall to  $<2 \mu\text{g}/\text{cm}^2$  and the VRLs for 21 of the 22 APIs tested would be  $<4 \mu\text{g}/\text{cm}^2$ .

The dependence of the VRL on light intensity was both more dramatic and more predictable for the APIs than for the excipients. Of the 22 APIs tested, 15 of the limits were the same regardless of the light intensity (see Table V). Only one of the lim-

its decreased slightly as light intensity increased and then subsequently increased as the light intensity was increased further. Six VRLs decreased with an increase in light intensity. Two of those decreases were small, similar to those seen with the excipients. However, as noted above, 4 compounds decreased from  $>5$  to  $<2 \mu\text{g}/\text{cm}^2$ . These data indicate that formulations containing these APIs might be candidates for a visual cleaning inspection, but light intensity would have to be considered. Either

a light source could be used or a light meter to verify the light intensity would be necessary.

An additional reason for testing marketed products was to compare the VRLs of the formulations with the VRLs of the individual formulation components. Twelve formulations were tested for their VRLs. The amount of API and excipients in a formulation differ. The amount spotted was based on the level of the API, which is the most potent compound in the formulation, rather than on the most-abundant excipient. Table VI shows a comparison of the VRLs of various marketed formulations compared with the individual components of the formulations. The VRLs for the formulations compared favorably with the limits for the individual components.

The VRL is of most value when it is below the ARL for the corresponding swab samples for the same compounds. The VRLs for the formulations from Table VI ranged from  $<0.33$  to  $<1.4 \mu\text{g}/\text{cm}^2$ . They are all significantly lower than the adulteration limit of  $4 \mu\text{g}/\text{cm}^2$ . Therefore, the margin of safety, *i.e.*, the difference between the VRL and the  $4 \mu\text{g}/\text{cm}^2$  limit, is reasonably wide. This indicates that these formulations might be candidates for visual cleaning inspection.

**Table VII: Variability of the visible-residue limits among observers.**

Observer variability re: light intensity (no. of observers)	Number of compounds
0	10
1	32
2	8
3	5
4	4
5	1

Although the VRLs were lower than the ARLs, using VRLs as cleaning validation acceptance criteria is still limited. The primary limitation for the use of VRLs is the training of the observer to inspect clean equipment. During this study, not only was there variability in the VRL based on the light intensity, there was also variability among the observers. Table VII shows the range of variability of the VRLs among the observers. Of the 59 detergents, excipients, APIs, and formulations tested, in only 10 of the cases did all four observers agree on the VRL. In more than 80% of the tests there was some difference of opinion as to what was visibly clean. Most of these differences were minor, but there were several cases that could be cause for concern.

For several of the excipients or APIs, a poorly trained observer or equipment inspector could incorrectly determine that a piece of equipment was clean when residue was above the ARL. This could potentially place a facility in violation of regulatory requirements.

It is far more likely, however, as evidenced from this study, that even a trained equipment inspector would determine that a piece of equipment needed further cleaning when it was, in fact, well below the ARL. That could lead to needless equipment

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re-cleaning, wasting resources, and adversely affecting production schedules.

## Conclusions

Using a visible-residue limit to verify equipment cleanliness is an intriguing concept. Determining that equipment is "visually clean" is a procedure that seems easy to document and that saves time and resources, both in terms of personnel and laboratory testing. To swab equipment, test the samples by HPLC, and document the results requires up to two person-days, occupies an HPLC overnight, and consumes several liters of solvents. To be able to look at a piece of equipment and sign a paper stating the equipment is "visually clean" is an attractive alternative.

Although implementing a cleaning program that relies on a visible-residue limit is an attractive possibility, extensive background work would be necessary to justify visible-residue limits, and other issues also would need to be addressed. Personnel training would be an ongoing requirement.

The procedure for introducing new development compounds, excipients, or formulations in the manufacturing area would have to be addressed. The resources necessary to introduce a visible residue limit program would be extensive, without assurance of acceptance by the regulatory agencies. However, using a visible-residue limit might be successfully argued for an application with limited scope such as introducing a new development compound into a pilot plant.

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