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2 **Our Mandate:**

3 The Inspectorate's mandate is to manage and deliver a national compliance and enforcement
4 program for blood and donor semen; cells, tissues and organs; drugs (human and veterinary);
5 medical devices and natural health products, collaborating with and across, all regions.
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8 **Health Products and Food Branch**
9 **Inspectorate**
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11 **Cleaning Validation Guideline**

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1.0 Introduction

This document provides some guidance on issues and topics related to cleaning validation. This topic reflects an area in pharmaceutical, biological and radiopharmaceutical manufacturing that is noted as being important by both the Inspectorate and the pharmaceutical industry. This guideline has been prepared to provide guidance to inspectors, evaluators and industry in reviewing the issues covered. Utilization of this information should facilitate compliance with Division 2 Part C of the *Food and Drug Regulations*.

It is not intended that the recommendations made in these guidelines become requirements under all circumstances. Information provided in the document for limits to be applied in defined circumstances, as well as the number of batches to be utilized for cleaning validation studies, is for guidance purposes only. Inspectors, evaluators and industry may consider other limits if proposed and documented in accordance with appropriate scientific justification.

2.0 Scope

This document on Cleaning Validation is intended to address special considerations and issues pertaining to validation of cleaning procedures for equipment used in the manufacture of pharmaceutical products, radiopharmaceuticals, and biological drugs. The document is also intended to establish inspection consistency and uniformity with respect to equipment cleaning procedures.

Principles incorporated in international guidance have been taken into account in the preparation of this document.

The document is intended to cover validation of equipment cleaning for the removal of contaminants associated with previous products, residues of cleaning agents as well as the control of potential microbial contaminants.

3.0 Principles

3.1 The objective of the cleaning validation is to verify the effectiveness of the cleaning procedure for removal of product residues, degradation products, preservatives, excipients, and/or cleaning agents as well as the control of potential microbial contaminants. In addition one would need to ensure there is no risk associated with cross-contamination of active ingredients.

3.2 Cleaning procedures must strictly follow carefully established and validated methods.

3.3 Appropriate cleaning procedures must be developed for all product-contact equipment used in the production process. Consideration should also be given to non-contact parts into which product may migrate (e.g., seals, flanges, mixing shaft, fans of ovens, heating elements, etc.).

136 3.4 Relevant process equipment cleaning validation methods are required for biological drugs
137 because of their inherent characteristics (proteins are sticky by nature), parenteral product
138 purity requirements, the complexity of equipment, and the broad spectrum of materials
139 which need to be cleaned.

140
141 3.5 Cleaning procedures for products and processes which are very similar do not need to be
142 individually validated. This could be dependent on what is common, equipment and
143 surface area, or an environment involving all product-contact equipment.
144

145 It is considered acceptable to select a representative range of similar products and processes. The
146 physical similarities of the products, the formulation, the manner and quantity of use by the
147 consumer, the nature of other product previously manufactured, the size of batch in comparison
148 to previously manufactured product are critical issues that justify a validation program.
149

150 A single validation study under consideration of the worst case can then be carried out which
151 takes account of the relevant criteria.
152

153 For biological drugs, including vaccines, bracketing may be considered acceptable for similar
154 products and/or equipment provided appropriate justification, based on sound and scientific
155 rationale, is given. Some examples are cleaning of fermenters of the same design but with
156 different vessel capacity used for the same type of recombinant proteins expressed in the same
157 rodent cell line and cultivated in closely related growth media; a multi-antigen vaccine used to
158 represent the individual antigen or other combinations of them when validating the same or
159 similar equipment that is used at stages of formulation (adsorption) and/or holding. Validation
160 of cleaning of fermenters should be done upon individual pathogen basis.
161

162 163 **4.0 Validation of Cleaning Processes** 164

165 4.1 As a general concept, until the validation of the cleaning procedure has been completed, the
166 product contact equipment should be dedicated.
167

168 4.2 In a multi-product facility, the effort of validating the cleaning of a specific piece of
169 equipment which has been exposed to several products and the cost of permanently
170 dedicating the equipment to a single product should be considered.
171

172 4.3 Equipment cleaning validation may be performed concurrently with actual production steps
173 during process development and clinical manufacturing. Validation programs should be
174 continued through full scale commercial production.
175

176 4.4 It is not considered acceptable to test-until-clean. This concept involves cleaning,
177 sampling, and testing with repetition of this sequence until an acceptable residue limit is
178 attained.
179

180 4.5 Products which simulate the physicochemical properties of the substance to be removed
181 may be considered for use instead of the substances themselves, when such substances are
182 either toxic or hazardous.
183

- 184 4.6 Raw materials sourced from different suppliers may have different physical properties and
185 impurity profiles. When applicable such differences should be considered when designing
186 cleaning procedures, as the materials may behave differently.
187
- 188 4.7 All pertinent parameters should be checked to ensure the process as it will ultimately be run
189 is validated. The procedures are detailed enough to cover all the cleaning parameters such
190 as:
- 191 i) the concentration of the cleaning agents,
 - 192 ii) the temperature of the cleaning solutions and water rinses,
 - 193 iii) the time of the cycle step e.g. cycle step counter, volume and flow rate of water
194 rinses;
 - 195 iv) the mechanism used to deliver the cleaning agent such as soaking or scrubbing for
196 manual cleaning or cycle parameters for automated cycles.
197
- 198 4.8 If automated procedures are utilized (Clean-In-Place: CIP), consideration should be given
199 to monitoring the critical control points and the parameters with appropriate sensors and
200 alarm points to ensure the process is highly controlled. Critical equipment and monitoring
201 devices should be calibrated.
202
- 203 4.9 During a campaign (production of several batches of the same product), cleaning between
204 batches may be reduced. The number of lots of the same product which could be
205 manufactured before a complete/ full cleaning is done should be determined.
206
- 207 4.10 Validation of cleaning processes should be based on a worst-case scenario including:
- 208
 - 209 i) Challenge of the cleaning process to show that the challenge soil can be recovered
210 in sufficient quantity or demonstrate log removal to ensure that the cleaning process
211 is indeed removing the soil to the required level, and
212
 - 213 ii) The use of reduced cleaning parameters such as overloading of contaminants, over
214 drying of equipment surfaces, minimal concentration of cleaning agents, and/or
215 minimum contact time of detergents.
216
- 217 4.11 At least three (3) consecutive applications of the cleaning procedure should be performed
218 and shown to be successful in order to prove that the method is validated. Equipment which is
219 similar in design and function may be grouped and a worst case established for validation.
220
221

222 **5.0 Equipment and Personnel**

223 **5.1 Equipment**

- 224
- 225
- 226 5.1.1 All processing equipment should be specifically designed to facilitate
227 cleanability and permit visual inspection and whenever possible, the equipment
228 should be made of smooth surfaces of non-reactive materials. Piping of the
229 equipment should be sloped continuously to ensure maximum drainability of the
230 lines; deadlegs should be avoided. For long transfer lines, removable sections

231 might be considered to evaluate the efficacy of the cleaning process by visual
232 and/or swab testing.

233
234 5.1.2 Critical areas (i.e., those hardest to clean) should be identified, particularly in
235 large systems that employ semi-automatic or fully automatic CIP systems.

236
237 5.1.3 Dedicated product-contact equipment should be used for products which are
238 difficult to remove (e.g., tarry or gummy residues in the bulk manufacturing), for
239 equipment which is difficult to clean (e.g., bags for fluid bed dryers), or for
240 products with a high safety risk (e.g., biologicals or products of high potency
241 which may be difficult to detect below an acceptable limit).

242
243 5.1.4 In a bulk process, particularly for very potent chemicals such as some steroids,
244 the issue of by-products needs to be considered if equipment is not dedicated.

245
246
247 **5.2 Personnel**

248
249 5.2.1 It is difficult to validate a manual cleaning procedure (i.e. an inherently
250 variable/cleaning procedure). Therefore, operators carrying out manual cleaning
251 procedures should be adequately trained, monitored, and periodically assessed.
252 Appropriate calibrated tools such as timers and measuring devices should be
253 available.

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256 **6.0 Microbiological Considerations**

257
258 6.1 Whether or not CIP systems are used for cleaning of processing equipment,
259 microbiological aspects of equipment cleaning should be considered. This consists largely
260 of preventive measures rather than removal of contamination once it has occurred.

261
262 6.2 There should be some documented evidence that routine cleaning and storage of equipment
263 do not allow microbial proliferation. For example, equipment should be dried before
264 storage, and under no circumstances should stagnant water be allowed to remain in
265 equipment subsequent to cleaning operations. Time-frames for the storage of unclean
266 equipment, prior to commencement of cleaning, as well as time frames and conditions for
267 the storage of cleaned equipment should be established.

268
269 6.3 The control of the bio-burden through adequate cleaning and storage of equipment is
270 important to ensure that subsequent sterilization or sanitization procedures achieve the
271 necessary assurance of sterility. This is also particularly important from the standpoint of
272 the control of pyrogens in sterile processing since equipment sterilization processes may
273 not be adequate to achieve significant inactivation or removal of pyrogens.

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278 **7.0 Documentation**

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- 7.1 Detailed cleaning procedure(s) are to be documented in SOPs
- 7.2 A Cleaning Validation Protocol is required to define how the cleaning process will be validated. It should include the following:
- i) The objective of the validation process;
 - ii) Responsibilities for performing and approving the validation study;
 - iii) Description of the equipment to be used;
 - iv) The interval between the end of production and the beginning of the cleaning procedure;
 - v) The number of lots of the same product, which could be manufactured during a campaign before a full cleaning is done;
 - vi) Detailed cleaning procedures to be used for each product, each manufacturing system or each piece of equipment;
 - vii) The number of cleaning cycles to be performed consecutively;
 - viii) Any routine monitoring requirement;
 - ix) Sampling procedures, including the rationale for why a certain sampling method is used;
 - x) Clearly defined sampling locations;
 - xi) Data on recovery studies where appropriate;
 - a. Validated analytical methods including the limit of detection and the limit of quantitation of those methods;
 - b. The acceptance criteria, including the rationale for setting the specific limits;
 - xii) Other products, processes, and equipment for which the planned validation is valid according to a “bracketing” concept;
 - xiii) Change Control/ Re-validation.
- 7.3 Depending upon the complexity of the system and cleaning processes, the amount of documentation necessary for executing various cleaning steps or procedures may vary.
- 7.4 When more complex cleaning procedures are required, it is important to document the critical cleaning steps. In this regard, specific documentation on the equipment itself which includes information about who cleaned it, when the cleaning was carried out, the product which was previously processed on the equipment being cleaned should be available. However, for relatively simple cleaning operations, the mere documentation that the overall cleaning process was performed might be sufficient.
- 7.5 Other factors such as history of cleaning, residue levels found after cleaning, and variability of test results may also dictate the amount of documentation required. For example, when variable residue levels are detected following cleaning, particularly for a process that is believed to be acceptable, one must establish the effectiveness of the process and of the operator performance. Appropriate evaluations must be made, and when operator performance is deemed a problem, more extensive documentation (guidance) and training may be required.

326 7.6 A Final Validation Report should be prepared. The conclusions of this report should state if
327 the cleaning process has been validated successfully. Limitations that apply to the use of
328 the validated method should be defined (for example, the analytical limit at which
329 cleanliness can be determined). The report should be approved by management.
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334 **8.0 Analytical Methods**

336 8.1 The analytical methods used to detect residuals or contaminants should be specific for the
337 substance or the class of substances to be assayed (e.g., product residue, detergent residue,
338 and/or endotoxin) and be validated before the cleaning validation study is carried out.
339

340 8.2 If levels of contamination or residual are not detected, it does not mean that there is no
341 residual contaminant present after cleaning. It only means that the levels of contaminant
342 greater than the sensitivity or detection limit of the analytical method are not present in the
343 sample.
344

345 8.3 In the case of biological drugs, the use of product-specific assay(s) such as
346 immunoassay(s) to monitor the presence of biological carry-over may not be appropriate
347 depending on the cleaning regime (e.g., use of caustics). Consideration should be given to
348 use of nonspecific assay methods (e.g. total organic carbon (TOC)) for the detection of
349 protein residue.
350

351 8.4 The analytical method and the percent recovery of contaminants should be challenged in
352 combination with the sampling method(s) used (see below). This is to show that
353 contaminants can be recovered from the equipment surface and to show the level of
354 recovery as well as the consistency of recovery. This is necessary before any conclusions
355 can be made based on the sample results. A negative test may also be the result of poor
356 sampling technique.
357
358

359 **9.0 Sampling, Rinsing, Rinse Samples and Detergents**

361 **Sampling**

363 9.1 There are two general types of sampling that are considered to be acceptable, direct
364 surface sampling (swab method) and indirect sampling (use of rinse solutions). A
365 combination of the two methods is generally the most desirable, particularly in
366 circumstances where accessibility of equipment parts can mitigate against direct surface
367 sampling.
368

369 **9.2 Direct Surface Sampling**

370
371 i) Areas hardest to clean and which are reasonably accessible can be evaluated by
372 direct sampling method, leading to establishing a level of contamination or

373 residue per given surface area. Additionally, residues that are "dried out" or are
374 insoluble can be sampled by physical removal.

375
376 ii) The suitability of the material to be used for sampling and of the sampling
377 medium should be determined. The ability to recover a sample accurately may
378 be affected by the choice of sampling material. It is important to assure that the
379 sampling medium and solvent (used for extraction from the medium) are
380 satisfactory and can be readily used.

381
382
383 9.3 Rinse Samples

384
385 i) Rinse samples allow sampling of a large surface area and of inaccessible systems
386 or ones that cannot be routinely disassembled. However consideration should be
387 given to the fact that the residue or contaminant may be insoluble or may be
388 physically occluded in the equipment.

389
390 ii) A direct measurement of the residue or contaminant in the relevant solvent
391 should be made when rinse samples are used to validate the cleaning process.

392
393 9.4 Indirect testing such as conductivity and TOC testing may be of some value for routine
394 monitoring once a cleaning process has been validated. This could be applicable to
395 reactors or centrifuge and piping between such large equipment can be sampled only
396 using rinse solution samples.

397
398 9.5 If the placebo method is used to validate the cleaning process then it should be used in
399 conjunction with rinse and/or swab samples. It is difficult to provide assurance that the
400 contaminant will be uniformly dispersed throughout the system or that it would be worn
401 off the equipment surface uniformly. Additionally, if the contaminant or residue is of
402 large enough particle size, it may not be uniformly dispersed in the placebo. Finally, the
403 analytical power of the assay may be greatly reduced by dilution of the contaminant.

404
405 9.6 It is important to use visual inspection in addition to analytical methodology to ensure the
406 process is acceptable.

407
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409 **Detergents**

410
411 9.7 When detergents are used in the cleaning process, their composition should be known to
412 the user and their removal should be demonstrated. The manufacturer should ensure that
413 they are notified by the detergent supplier of any changes in the formulation of the
414 detergent.

415
416 9.8 Detergents should be easily removable, being used to facilitate the cleaning during the
417 cleaning process. Acceptable limits should be defined for detergent residues after
418 cleaning. The possibility of detergent breakdown should also be considered when
419 validating cleaning procedures.

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Last Rinse

9.9 Water for injection should be used as the last rinse for product-contact equipment to be utilized in the fabrication of sterile products.

9.10 Purified water is considered acceptable as the last rinse for product-contact equipment used in the fabrication of non-sterile products or sterile products for ophthalmic use.

Note: Because of the presence of varying levels of organic and inorganic residues as well as of chlorine, tap water should not be used in the last rinse of any cleaning procedure for product-contact equipment.

10.0 Establishment of Limits

10.1 The fabricator's rationale for selecting limits for product residues should be logical and based on the materials involved and their allergenicity, toxicity and potency. The limits should be practical, achievable, and verifiable.

10.2 The main active compound may be degraded during the cleaning process by hot, aqueous, alkaline and acidic cleaning solutions. In establishing product residual limits, it may not be adequate to focus only on the main reactant since by-products/chemical variations (active decomposition material) may be more difficult to remove or be detected by specific analytical methods.

10.3 The approach for setting limits can be:

- i) product specific cleaning validation for all products;
- ii) grouping into product families and choosing a worst case product;
- iii) grouping by properties (e.g., solubility, allergenicity, potency, toxicity or formulation ingredients known to be difficult to clean);
- iv) setting limits on not allowing more than a certain fraction of carryover;
- v) different safety factors for different dosage forms.

10.4 No residue is visible on the equipment after cleaning procedures are performed. Carry-over of product residues should meet defined criteria for example the most stringent of the following criteria:

- i) NMT 0.1% of the minimum daily therapeutic dose of any product to appear in the maximum daily dose of the following product;
- ii) NMT 10 ppm of any product to appear in another product.

Carry-over of product residue is calculated for the shared equipment surface area between products. A shared surface area is considered to be all of the product contact surface area for the entire manufacturing process. A manufacturing operation may use several pieces of equipment as part of an equipment train (examples: powder blender, dryer, compressing machine, coating equipment, etc...); in this case, the sum of all residues accumulated on each piece of equipment

469 should be considered. Additionally, it may be necessary to determine residue limits for each
470 individual piece of equipment.

471
472 In the absence of product specific cleaning validation data, the matrix approach should consider
473 product grouping such that the allowable carryover in each grouping should be based on
474 applying the sum of the residues obtained for the hardest to clean product(s) to the most active
475 (e.g. lowest therapeutic dose) compound in that group.

476
477 For products with multiple active ingredients, unless specific data are acquired, it should be
478 assumed that all carryover is the most active substituent.

479
480 For genotoxic product residues:

- 481
- 482 i) when sufficient evidence for a thresholded genotoxicity is available, exposure
483 levels can be established according to the procedure as outlined in the Appendix
484 3 of the EMEA Guideline on the Limits of Genotoxic Impurities (2006),
 - 485
 - 486 ii) when no threshold mechanisms are identified, a threshold of toxicological
487 concern of 1.5 µg/day is acceptable. A higher level may be acceptable upon
488 scientific justification.
 - 489

490 The microbiological and pyrogen limits are scientifically justified for the type of products being
491 manufactured and ensure that the quality of the product is not impaired by the cleanliness of the
492 equipment.

- 493
- 494 10.5 Self-contained facilities are required for:
- 495 i) certain classes of highly sensitizing drugs such as penicillins and cephalosporins.
 - 496
 - 497 ii) other classes of highly potent drugs such as potent steroids, cytotoxics, or
498 potentially pathogenic drugs (e.g., live vaccines), for which validated cleaning or
499 inactivation procedures cannot be established (e.g., the acceptable level of
500 residue is below the limit of detection by the best available analytical methods).
501 Input from a toxicologist may be necessary.
 - 502

503

504 **11.0 Change Control / Revalidation**

505

506 11.1 A change control system is in place to ensure that all changes that might impact the
507 cleaning process are assessed and documented. Significant changes should follow
508 satisfactory review and authorization of the documented change proposal through the
509 change control procedure. Minor changes or changes having no direct impact on final or
510 in-process product quality should be handled through the documentation system. The
511 review should include consideration of re-validation of the cleaning procedure.

512

513 11.2 Changes which should require evaluation and likely re-validation include but are not
514 limited to:

- 515 i) Changes in the cleaning procedure;
- 516 ii) Changes in the raw material sources;

- 517 iii) Changes in the formulation and/or process of products;
- 518 iv) New products;
- 519 v) Changes in the formulation of detergents;
- 520 vi) New detergents;
- 521 vii) Modifications of equipment.

522
523 11.3 The cleaning process should be reassessed at defined intervals, and re-validated as
524 necessary. Manual methods should be reassessed at more frequent intervals than clean-
525 in-place (CIP) systems.
526

527 528 **12.0 References**

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565 **13.0 Appendix A: Sample Calculation of the Carryover Limits**

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Example 1

Products A and B are manufactured using an equipment train which consists of a blender, a milling machine, a compressing machine and a filling machine.

Equipment	Product A	Product B
Blender	X	X
Milling machine	X	X
Compressing machine	X	X
Filling machine	X	X

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574

Product's characteristics:

Product	API/ tablet (mg)	Tablet weight (mg)	Batch size (kg)	Minimum daily therapeutic dose (TD _{min}), mg of API	Maximum daily therapeutic dose (TD _{max}), mg of API
A	10	50	200	5	20
B	15	75	120	15	60

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Equipment	Surface area, cm ²
Blender	160 000
Milling machine	30 000
Compressing machine	40 000
Filling equipment	20 000
Total, equipment train	250 000

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Equipment is cleaned according to cleaning procedures after each use. No residue is visible on the equipment after cleaning.

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583

Question 1: What is the maximum allowable carryover (MAC) of residue A on the equipment train used to manufacture product B based on therapeutic dose, Product B being manufactured after Product A?

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$$MAC_{A,TD} = \frac{MTD_A \times BS_B}{MDD_B \times SF}$$

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- MAC_{A,TD} Maximum allowable carryover of product A based on therapeutic dose
- TD_{min,A} Minimum daily therapeutic dose of product A expressed as weight of API.
- BS_B Batch size of product B (120 kg or 120 000 000 mg)
- TD_{max,B} Maximum daily dose of product B expressed as total weight of tablets.
- SF Safety factor, 1000 (0.1% therapeutic dose)
- TD_{min,A} is 5 mg (minimum daily therapeutic dose), even the 10 mg tablet is manufactured.

595 The $TD_{\max,B}$ is 60 mg of API which represents 4 tablets. The total weight of 4 tablets is 300 mg
596 (4 tablets x 75 mg/tablet).

597
598 $MAC_{A,TD} = \frac{5 \text{ mg} \times 120\,000\,000 \text{ mg}}{300 \text{ mg} \times 1000} = 2000 \text{ mg}$
599

600
601
602 *Question 2: What is the maximum allowable carryover (MAC) on the equipment train used to*
603 *manufacture product B based on 10 ppm limit, Product B being manufactured after Product A?*
604

605 $MAC_{A,ppm} = 10 \text{ ppm} \times BS_B$

606 $MAC_{A,ppm}$ Maximum allowable carryover of residue A based on ppm limit

607 BS_B Batch size of product B (120 kg or 120 000 000 mg)

608
609 $10 \text{ ppm} = 0.00001 \text{ (mg/mg)}$

610 $MAC_{A,ppm} = 0.00001 \text{ (mg/mg)} \times 120\,000\,000 \text{ mg} = 1200 \text{ mg}$

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612
613 *Question 3: What is the acceptable swab limit for this equipment train?*

614
615 According to the guide, carry-over of product residues should meet defined criteria, for example
616 the most stringent of the following criteria:

- 617
618 (i) NMT 0.1% of the minimum daily therapeutic dose of any product to appear in the
619 maximum daily dose of the following product;
- 620 (ii) NMT 10 ppm of any product to appear in another product.

621 The Maximum allowable carryover on this equipment train is 1200 mg (smallest amount
622 between 2000 mg and 1200 mg). The acceptable swab limit is 1200 mg per 250 000 cm^2 or 4.8
623 $\mu\text{g}/\text{cm}^2$.

624
625
626 **Example 2**

627
628 Products A and B are manufactured using an equipment train which consists of a blender, a
629 milling machine, a compressing machine and a filling machine. The same compressing machine
630 and filling machine are used to compress and package product C.

631

Equipment	Product A	Product B	Product C
Blender	X	X	
Milling machine	X	X	
Compressing machine	X	X	X
Filling machine	X	X	X

632
633 Product's characteristics:
634

Product	API/ tablet (mg)	Tablet weight (mg)	Batch size (kg)	Minimum daily therapeutic dose (TD _{min}) (mg of API)	Maximum daily therapeutic dose (TD _{max})(mg of API)
A	10	50	200	5	20
B	15	75	120	15	60
C	2	95	150	1	4

635

636

Equipment	Surface area, cm ²
Blender	160 000
Milling machine	30 000
Compressing machine	40 000
Filling equipment	20 000
Total, equipment train	250 000

637

638

639 Equipment is cleaned according to procedures after each use. No residue is visible on the
640 equipment after cleaning.

641

642

643 *Question 1: What is the maximum allowable carryover (MAC) of residues A and C on the*
644 *equipment train used to manufacture product B based on therapeutic dose, assuming that the*
645 *sequence used in the manufacturing is Product A, C and B and product C is more potent than*
646 *product A?*

647 The minimum therapeutic dose of Product C should be used in the formula for the calculation of
648 the sum of residues A and C since Product C is more potent than Product A.

649

$$650 \text{MAC}_{A+C,TD} = \frac{\text{MTD}_C \times \text{BS}_B}{\text{MDD}_B \times \text{SF}}$$

651

652

653 $\text{MAC}_{A+C,TD}$ Maximum allowable carryover of the sum of residues A and C based on
654 therapeutic dose of product C

655 $\text{TD}_{\min,C}$ Minimum therapeutic dose of product C expressed as weight of API.

656 BS_B Batch size of product B (120 kg or 120 000 000mg)

657 $\text{TD}_{\max,B}$ Maximum daily dose of product B expressed as total weight of tablets.

658 SF Safety factor, 1000 (0.1% therapeutic dose)

659

660 $\text{TD}_{\min,A}$ is 1mg (minimum daily therapeutic dose), even the 2mg tablet is manufactured.

661

662 The $\text{TD}_{\max,B}$ is 60 mg of API which represents 4 tablets. The total weight of 4 tablets is 300 mg
663 (4 tablets x 75 mg/tablet)

664

$$665 \text{MAC}_{A+C,TD} = \frac{1 \text{ mg} \times 120\,000\,000 \text{ mg}}{300 \text{ mg} \times 1000} = 400 \text{ mg}$$

666

667

668 *Question 2: What is the maximum allowable carryover (MAC) of residues A and C on the*
669 *equipment train used to manufacture product B based on 10 ppm limit, assuming that the*

670 *sequence used in the manufacturing is Product A, C and B and product C is more potent than*
671 *product A?*

672
673 $MAC_{A+C,ppm} = 10 \text{ ppm} \times BS_B$
674 $MAC_{A+C,ppm}$ Maximum allowable carryover of the sum of residues A and C based on ppm limit
675 BS_B Batch size of product B (120 kg or 120 000 000mg)

676
677 $10 \text{ ppm} = 0.00001 \text{ (mg/mg)}$
678 $MAC_{A+C,ppm} = 0.00001 \text{ (mg/mg)} \times 120\,000\,000 \text{ mg} = 1200 \text{ mg}$

679
680 *Question 3: What is the acceptable swab limit for this equipment train?*
681 The most stringent limit of the Maximum allowable carryover based on therapeutic dose and 10
682 ppm limit is 400 mg (smallest amount between 1200 and 400 mg).
683 The acceptable swab limit is $400 \text{ mg}/250\,000 \text{ cm}^2$ or $1.6 \mu\text{g}/\text{cm}^2$.

684
685 *Question 4: The following swab residue results are obtained according an approved protocol. Is*
686 *it acceptable?*

	Surface area (cm ²)	Residue A (mg)	Residue C (mg)
Blender	160 000	100	
Milling machine	30 000	45	
Compression machine	40 000		75
Filling machine	20 000		25

687
688 The swab results for:
689 - the Blender is $100 \text{ mg}/160\,000 \text{ cm}^2$ or $0.63 \mu\text{g}/\text{cm}^2$.
690 - the Milling machine: $45 \text{ mg}/30\,000 \text{ cm}^2$ or $1.5 \mu\text{g}/\text{cm}^2$
691 - the Compressing machine: $75 \text{ mg}/40\,000 \text{ cm}^2$ or $1.88 \mu\text{g}/\text{cm}^2$
692 - the Filling machine: $25 \text{ mg}/20\,000 \text{ cm}^2$ or $1.25 \mu\text{g}/\text{cm}^2$

693
694 The total of residues A and C (245 mg) is lower than the total limit allowable for this equipment
695 train (400 mg). However, the residue result for the compression machine exceeds the acceptable
696 swab limit for this train ($1.6 \mu\text{g}/\text{cm}^2$). It may be a good practice to set a limit per swab for
697 equipment and parts which are more difficult to clean, in addition to the total limit allowable of
698 residues for an equipment train.