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3 Our mandate :

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5 The Inspectorate's mandate is to manage and deliver a national compliance and enforcement program for blood and donor semen;  
6 cells, tissues and organs; drugs (human and veterinary); medical devices and natural health products, collaborating with and across,  
7 all regions.  
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# 12 Health Products and Food Branch Inspectorate

## 13 14 Process Validation : 15 Terminal Sterilization Processes 16 for Pharmaceutical Products (GUI-0074)

17  
18  
19 Supersedes :

20 Process Validation : Gaseous Sterilization for Pharmaceuticals (GUI-0007),  
21 Process Validation : Irradiation Sterilization for Pharmaceuticals (GUI-0009), and  
22 Process Validation : Moist Heat Sterilization for Pharmaceuticals (GUI-0010)  
23

24 Date issued :

25  
26  
27 Date of implementation :

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29  
30 Ce document est aussi disponible en français.  
31

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36 *compliance by the regulated party with the Act, the Regulations and the applicable administrative policies.*  
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## 1. Introduction

The goal of validation is to demonstrate that a process, when operated within established limits, produces a product of consistent and specified quality. During validation, the critical process parameters must be identified, and, based on sound scientific principles, appropriate studies must be performed to demonstrate that the parameters can be met on a consistent basis.

Process validation must be considered as early in the development of a new product or a new or modified process as is practical. In this way, data required for validation can be collected during development studies, and also during the production of clinical and commercial batches. This "prospective" validation approach is preferred by the Inspectorate and other Directorates since it demonstrates a well thought-out product production process.

In preparing this document, we have assumed that the reader is familiar with the applications, limitations, and effects of all methods of terminal sterilization including moist heat, radiation, and gaseous sterilization.

The objective of any processes pertaining to terminal sterilization is to control the pre-sterilization bioburden to an appropriate level. It is important that the level of microbial quality be critically evaluated first, in order that the use of the terminal sterilization process may be rationally applied. Knowledge of the microbial quality of the materials and components has significant importance. A reduction of the microbial bioburden of these materials and components will allow for a more effective terminal sterilization. The probability of survival is a function of the number and resistance of microorganisms present on the product. It is important to track the species as well as the number of organisms in order to assure that the terminal sterilization parameters continue to provide the same Sterility Assurance Level (SAL).

This document replaces the previous version of *Process Validation: Gaseous Sterilization for Pharmaceuticals* (GUI - 0007), *Process Validation : Irradiation Sterilization for Pharmaceuticals* (GUI - 0009) and *Process Validation: Moist Heat Sterilization for Pharmaceuticals* (GUI- 0010).

The content of this document should not be regarded as the only acceptable approach to validation of sterilization processes, nor does it intend to cover every conceivable case. Alternative approaches to validation can be considered with the appropriate scientific justification. Different approaches may be called for as new technologies emerge.

## 2. Purpose

The purpose of this document is to provide guidance to manufacturers of pharmaceutical dosage forms regarding how to establish the scientific effectiveness, as required by the Health Products and Food Branch Inspectorate (HPFBI). This guidance is designed to facilitate compliance by regulated industry and to enhance consistency in application of the regulatory requirements.

## 3. Scope

This guidance applies to the validation of sterilization of raw materials, packaging materials, and finished products for pharmaceutical and veterinary drugs. This guidance is also applicable to the subset of biological drugs that are not negatively impacted by the sterilization process described.

## 4. Validation approaches

- 4.1 The validation of a product-specific sterilizing process may be performed using either the Prospective or Concurrent Validation approach. Sterilization is an example of a process for which efficacy cannot be verified by retrospective evaluation of documentation and testing of the product. It is important to be aware that exposure to a validated and accurately controlled sterilization process is not the only factor associated with the provision of assurance that the product is sterile and suitable for its intended use. The most appropriate approach should be selected, and this selection must be justified and documented. Please refer to [Validation Guidelines for Pharmaceutical Dosage Forms \(GUI-0029\)](#) for this selection. The validation is conducted, documented and evaluated, and the validation process and end-product is approved by the validation team.

- 138 4.1.1. Prospective Validation of the sterilization process applies when new products or new formulations of  
139 existing products are being developed or when a change is made to an existing sterilization process  
140 that may affect the quality or the sterility of a drug.  
141
- 142 4.1.2 Concurrent Validation of the sterilization process applies to existing products when an intended  
143 change other than to the sterilization process is expected to have no effect on the quality or the sterility  
144 of a drug.  
145

## 146 **5. Protocol development and control**

- 147
- 148
- 149 5.1 Validation of a product specific sterilization process must be based on detailed protocol that is approved prior  
150 to execution.  
151
- 152 5.2 Changes to the validation protocol require a written change control procedure. The purpose of the change  
153 control procedure should be to reduce the risk of unauthorized deliberate, or inadvertent change(s) being made  
154 to the protocol, methods and/or procedures, the sterilization process, and the product/materials/supplies.  
155
- 156 5.3 The Process Validation Protocol should contain:
- 157
- 158 5.3.1 a detailed description of the sterilization process and environment ;
- 159
- 160 5.3.2 the process objectives in terms of product type, batch size, container/closure system, and the  
161 required Sterility Assurance Level (SAL) ;  
162
- 163 5.3.3 pre-established specifications and parameters for the sterilization process such as:  
164 temperature limits, minimum/maximum exposure, maximum acceptable pre-sterilization  
165 product bioburden, etc. ;  
166
- 167 5.3.4 a description of the equipment and relevant support systems which will be used for the  
168 sterilization process. This description should include or refer to relevant performance  
169 characteristics of each system, sub-system or piece of equipment such as gauge sensitivity  
170 and response, valve operation, alarm system functions, timer response and accuracy, cycle  
171 controller functions, air break systems and filters ;  
172
- 173 5.3.5 requirements for equipment calibration ;
- 174
- 175 5.3.6 a description of the methodology for monitoring the performance of the equipment and the  
176 entire sterilization process with a defined sequence and timing of activities ;  
177
- 178 5.3.7 a list and description of all validated test methods, in-process controls, sampling procedures,  
179 and tabulation of data collected ;  
180
- 181 5.3.8 a listing of the personnel responsible for coordinating, performing, evaluation and certifying  
182 each activity identified in the protocol ;  
183
- 184 5.3.9 any additional information that may be relevant to the sterilization process.  
185

## 186 **6. Personnel**

187 Validation should be planned, performed, and evaluated by qualified personnel who have received appropriate training  
188 and possess relevant experience.  
189  
190  
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192

## 7. Data review and study certification

- 193  
194  
195 7.1 All information and data generated as part of the validation program must be evaluated by qualified individuals  
196 against protocol requirements, and judged as meeting or failing these requirements.  
197  
198 7.1.1 The evaluations should be performed-in a timely manner.  
199  
200 7.1.2 If evaluations show that protocol requirements were not met, the impact on the sterilization process  
201 should be investigated and documented. The change control procedure must be followed when  
202 protocol modifications are necessary.  
203  
204 7.1.3 Failure to adhere to the procedure or criteria as laid down in the validation protocol must be considered  
205 as potentially compromising the validity of the study itself, and requires critical evaluation of the impact  
206 on the study.  
207  
208 7.2 The final certification of a process validation study must indicate acceptance or rejection of the process  
209 parameters.  
210

## 8. Laboratory

211  
212 All laboratory tests, including  $D_{value}$  determinations of microbial species must be performed by a competent  
213 laboratory that complies with regulatory requirements. Laboratory tests must be validated and detailed  
214 methodology must be available in writing.  
215  
216  
217

## 9. Equipment

- 218  
219  
220 9.1 Equipment specification  
221  
222 9.1.1 Ethylene Oxide Equipment specification  
223  
224 The specification for the equipment should be developed and documented and should include the  
225 preconditioning area, the sterilizer, and the aeration environment. It should include at minimum:  
226 - description of the equipment  
227 - composition of the sterilizing agent and means by which it is delivered to the chamber  
228 - description of any other gases used in the process and the means by which they are delivered to the  
229 chamber  
230 - purity and quality of steam  
231 - description of instrumentation for monitoring, controlling and recording the sterilization process,  
232 including sensors characteristics and their locations  
233 - description and validation status of software used to control/monitor the process  
234 - assurance that failure in control function does not lead to failure in recording of process parameters  
235 such that an ineffective process appears effective (fail safe feature) .  
236  
237 9.1.2 Moist heat equipment specification  
238  
239 Equipment used to deliver the sterilization process should be specified and should include at  
240 minimum :  
241 - materials of construction  
242 - control, monitoring, recording devices (control instrumentation should be independent of monitoring  
243 instruments and recording charts)  
244 - description and validation status of software used to control/monitor the process  
245 - safety features for environmental protection and control of personnel  
246 - location, space and environment in which the equipment is to be installed.  
247  
248  
249

250  
251 9.1.3 Irradiator specification  
252

253 The following should be specified at minimum :

- 254 - the irradiator, its characteristics and method of operation
- 255 - software used to control and monitor the process
- 256 - description and validation status of software used to control/monitor the process
- 257 - location of the irradiator within the premises
- 258 - conveyor system, its operation, construction and range of speed
- 259 - construction of irradiation containers
- 260 - for gamma irradiators, the type of radionuclide and the geometry of the gamma source
- 261 - for electron beam and X-ray irradiators, the characteristics of the beam (electron energy, scan width  
262 and uniformity) .

263  
264 Prior to commencing validation studies, it is necessary that the equipment be checked and certified as properly  
265 equipped, installed and operating as per its design. Further guidance on conducting equipment qualification is available  
266 in the Health Canada guideline entitled [Validation Guidelines for Pharmaceutical Dosage Forms \(GUI-0029\)](#) .  
267

268 9.2 Installation qualification  
269

270 The installation qualification must include verification of requirements for all the construction materials, the  
271 sizes and tolerances of the equipment, support services, power supplies, the alarm systems, monitoring  
272 systems with response tolerance and accuracy requirements, and the operational parameter requirements as  
273 governed by the established specifications.  
274

275 9.3 Operational qualification  
276

277 Operational qualification demonstrates that controls, alarms, monitoring devices and operation indicators  
278 function properly; chamber conditions and integrity are maintained; written procedures accurately reflect  
279 equipment operation; and operational parameters are attained as pre-set for each test run.  
280

281 9.4 Equipment calibration  
282

283 9.4.1 The range, sensitivity, accuracy, reproducibility, and response-time of all controlling, monitoring, and  
284 recording equipment must be adequate to demonstrate that defined process conditions are met.  
285

286 9.4.2 All equipment must be calibrated and/or certified before any process validation can be performed. The  
287 standards used for calibration must be traceable to an appropriate standard. Documented evidence  
288 must be available for equipment calibration.  
289

290 9.4.2.1 Sterilization by moist heat and dry heat  
291

292 Equipment common to heat sterilization processes include temperature recorders and  
293 sensors, thermocouples, pressure sensors for jacket and chamber pressure, timers,  
294 conductivity monitors for cooling water, flow meters for water/steam, water level indicators,  
295 thermometers including those for thermocouple reference, and chamber monitoring.  
296

297 9.4.2.2 Sterilization by irradiation  
298

299 Equipment common to both electron beam and gamma radiation processing technologies  
300 include dosimeters, spectrophotometers, thickness gauges, timers and recorders.  
301

302 9.4.2.3 Sterilization with ethylene oxide and other gases  
303

304 Equipment common to gas sterilization include recorders, thermocouples, pressure and  
305 humidity sensors, timers, gas analyzers and balances.  
306

- 307 9.4.3 Re-calibration must be performed as required and documented after any significant equipment  
308 maintenance.  
309

## 310 10. Facilities

- 311  
312 10.1 All facilities using terminal sterilization processes must meet conditions described in the Health Canada  
313 guideline entitled [Good Manufacturing Practices \(GMP\) Guidelines - 2009 Edition, Version 2 \(GUI-0001\)](#).  
314 Additional considerations are described below as applicable.  
315

- 316 10.2 Facility qualification for sterilization by irradiation  
317

318 Prior to commencing any studies it is necessary to qualify the facility. The facility qualification focuses on the  
319 design, installation, and operations.  
320

- 321 10.2.1 Facility design and installation  
322

323 Qualification begins with the establishment of design, and installation requirements.  
324

- 325 10.2.1.1 Design : Included in these written requirements are : the key construction materials,  
326 the source of ionizing radiation, product transportation system through the irradiator,  
327 support services and power supplies, control systems, monitoring and alarm systems  
328 with response tolerance and accuracy requirements, and performance specifications.  
329 All of these requirements must be compatible with the product, the product format, and  
330 the established process specifications.  
331

- 332 10.2.1.2 Commissioning/re-commissioning of the facility should be based on written procedures  
333 that ensures design changes are documented in the " as built/as installed " drawings  
334 and in all manuals, and that the performance specifications are met.  
335

- 336 10.2.1.3 All design/installation parameters should be documented and certified prior to  
337 operational qualification of the equipment.  
338  
339

## 340 11. General considerations prior to process validation

- 341  
342 11.1 The product definition, in terms of physical, chemical, microbial and pharmacological properties should be  
343 established prior to validation.  
344

- 345 11.2 Studies should be completed to determine bioburden in the materials to be sterilized. These studies should  
346 also include evaluation of the impact of hold times on the bioburden.  
347

- 348 11.3 Specifications for raw materials and packaging components should be established.  
349

- 350 11.4 The required SAL should be determined.  
351

- 352 11.5 The compatibility of the sterilization process with the items to be sterilized should be evaluated.  
353

- 354 11.6 Validation of analytical methods should be complete with adequate calibration and qualification of measuring  
355 equipment used in analytical methods and measurement of process parameters in operation of the sterilization  
356 cycle.  
357

- 358 11.7 Indicating devices used in the validation studies or used as part of post-validation monitoring or requalification  
359 must be calibrated, appropriately stored and used before their expiry date.  
360

- 361 11.7.1 Physical and chemical indicators must be tested to demonstrate adequate pre-determined response to  
362 both time and exposure. Detailed written test procedures and records of test results must be available.  
363

- 364 11.7.2 Biological indicators must be tested according to detailed written procedures for viability and  
365 quantitation of the challenge organism and for the time and exposure response. This applies to  
366 indicators either prepared in-house or obtained commercially.
- 367 11.7.3 For commercial indicators, a certificate of testing for each lot indicating the  $D_{\text{value}}$  of the lot must be  
368 available. The quantitation is acceptable if the biological indicator manufacturer's count has been  
369 qualified and periodically confirmed as per written procedures.
- 370
- 371 11.7.4 Records of the testing for the biological indicators must be available.
- 372
- 373 11.7.5 When qualifying commercial or in-house biological indicators the choice of media (pH, electrolytes,  
374 carbohydrates, etc.) and sample carriers (suspension in ampoules, paper strips, inoculated products  
375 and inoculation on solid carriers) must be consistent with the materials used in the terminal sterilization  
376 process.
- 377

## 378 11.8 Sterilization cycle development

379

380 Two basic approaches are employed to develop sterilization cycles for terminal sterilization processes :  
381 Overkill and Probability of Survival. Microbial performance qualification may be required prior to introduction of  
382 new or altered products or when there are changes in packaging, loading patterns, equipment, process  
383 parameters, or bioburden based on seasonal variation or routine monitoring.

384

385 11.8.1 The Overkill method is used when the product can withstand prolonged exposure to the sterilization  
386 process without adverse effects

387

388 11.8.2 The Probability of Survival approach is used when there are limitations to exposure to the sterilization  
389 parameters. In this approach, the process for the terminal sterilization is validated to achieve the  
390 destruction of the pre-sterilization bioburden with a minimum safety factor of an additional six-log  
391 reduction ( $10^{-6}$ ) . The probability that any one unit is contaminated is therefore no more than one in a  
392 million; this is considered to be an acceptable level of sterility assurance.

393

394 11.8.2.1. The probability of survival is determined using a semi-logarithmic microbial death  
395 curve, where a plot of the log of the number of survivors versus time at a fixed  
396 exposure yields a straight line. After the line has crossed below  $10^0$  (less than one  
397 survivor) , the y-value corresponding to a given time or dose value is expressed as the  
398 probability of survival.

399

400 11.8.2.2 The determination of the minimum  $F_0$  value for the Probability of Survival approach is  
401 based upon the number of microorganisms (bioburden) found in a given product and  
402 when applicable their heat resistance.

403

## 404 11.9 Cycle interruptions

405

406 It is necessary to specify for each product, the maximum permitted length of time from the completion of  
407 packaging to the commencement of the sterilization treatment. Normally, all of a production lot of a  
408 pharmaceutical would be simultaneously exposed to the gamma radiation source. (There will be some  
409 exceptions for larger volumes/bulkier drugs.) Where multiple sterilization cycles are required or where each  
410 unit is individually exposed, this period would be from the start of processing the first unit until the last unit has  
411 been sterilized.

412

## 413 12. Biological challenge reduction studies

414

415

416 12.1 The sterilization cycle is assessed by introducing a known quantity of specific microorganisms with established  
417  $D_{\text{values}}$  and assessing the level of reduction with time. A probability of survival of less than 1 in  $10^6$  is confirmed  
418 in all cases.

419

420 12.2 The level of biological challenge selected for the study should consider product lot-to-lot variation in the  
421 bioburden (species and number) .

422  
423 12.3 A worst-case bioburden challenge using an appropriate organism as described within the below table is  
424 acceptable. In all other cases the microorganism with the highest  $D_{value}$ , occurring in the natural population as  
425 determined by sampling of the environment, should be used. Justification should be available to support its  
426 use.

427  
428 Table 1 : Organisms for Biological Challenges

Sterilization Method	Recommended Organism
Moist Heat	Geobacillus stearothermophilus
Irradiation	Bacillus pumilus
Ethylene Oxide	Bacillus atrophaeus

443  
444  
445 12.4 The level of biological challenge selected for the study should consider seasonal environmental variation as  
446 well as lot-to-lot variation in the product bioburden (quantity) and  $D_{value}$ .

447  
448 12.5 Positive controls should be run with each load to verify the viability of the challenge organism.

449  
450 12.6 The biological challenge may be run in conjunction with distribution studies/penetration studies.

451  
452 12.7 The placement of biological challenges must be defined in writing. The challenge should be located as close as  
453 possible to worst case locations and placed as close as possible to any sensors if run concurrent with  
454 distribution studies/penetration studies. The challenge should be placed in containers where practicable, so as  
455 to reflect the desired processing conditions.

456  
457 12.8 A minimum of three cycles should be performed for each load configuration under evaluation.

458  
459 12.9 Records of the organism type,  $D_{value}$ , challenge level, lot number, placement, and growth result  
460 should be available.

461  
462 12.10 Growth of any challenge following any of the runs indicates that sterilization has not been achieved.  
463 In such cases, the process parameters must be evaluated. If no processing error is discernable, the  
464 sterilization process must be considered unacceptable.

465  
466 12.11 When documented change control evaluation indicates a potential adverse effect on the sterilization  
467 method, the biological challenge studies should be repeated.

### 468 469 470 **13. Process validation : Sterilization by moist heat**

#### 471 472 13.1 Introduction

473  
474 The Inspectorate recognizes that terminal moist heat sterilization, when practical, is presently considered the  
475 method of choice to ensure sterility. For the purpose of ensuring drug sterility, all aqueous-based products  
476 intended to be sterile, should be subject to terminal moist heat sterilization except for instances where;

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- 13.1.1 Terminal moist heat sterilization is not practical because it results in product or packaging degradation. Such instances of degradation are to be fully evaluated and documented.
- 13.1.2 Validated aseptic processes that exclude human intervention such as robotics, form-fill-seal and full barrier systems (isolators) are used.
- 13.2 Product Definition
- 13.2.1 Product and product packaging system to be sterilized shall be characterized. All aqueous-based products intended to be sterile are subject to terminal moist heat sterilization.
- 13.2.2 If a process challenge device (PCD) is identified as a challenge that can be used to represent the product and its packaging system, it should be defined.
- 13.2.3 If a level of moisture present in the product/packaging system prior to sterilization process could affect the efficiency of the sterilization process, the limit value should be specified
- 13.2.4 When process parameters are defined using a bioburden base method, an estimation of bioburden may be included to ensure that the condition of the product and its packaging system presented for sterilization will not compromise the effectiveness of the sterilization process.
- 13.2.5 The item to be sterilized, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents re-contamination after sterilization. All parts of the load should be in contact with the sterilizing agent at the required temperature for the required time.
- 13.3 Sterilizing agent (steam) characteristics
- The specification for a saturated steam sterilization process has to include at minimum :
- the holding time and the minimum and maximum temperatures and their locations measured during this time in an empty sterilizer chamber
  - during the holding time, the maximum difference between the temperature measured at the reference measuring point and the theoretical steam temperature determined from steam table values (for measured sterilizer chamber pressure)
  - the reference loads to be used to evaluate the effectiveness of the sterilization process
  - description of the monitoring device, its location, and interpretation of results if used to verify delivery of specified sterilization process.
  - steam used for sterilization has to be of suitable quality (does not contain additives at a level to cause contamination of product or equipment).
- 13.4 Sterilization Process Definition
- The sterilization process has to be specified including :
- a description of the operating cycle
  - process parameters and their tolerances - both pressure and temperature should be used to monitor the process (physical process parameters should be measured to confirm reproducibility)
  - requirement for the conditioning of product prior to sterilization
  - location of reference measuring point
  - minimum and maximum pressure in sterilizing chamber
  - falling and rising pressure gradient and tolerances
  - maximum quantity of each contaminant present in any liquid, air, gas, steam admitted to sterilizer chamber
  - load configuration
  - restrictions on size and mass of the load
  - location and acceptance criteria for BIs and CIs
  - minimum cycle lethality achieved throughout the sterilization load

- minimum level of sterility assurance (SAL) to be achieved by sterilization process has to be specified. It can be based on knowledge of bioburden or determined by an "overkill" method.

### 13.5 $F_0$ and $D_{\text{value}}$

13.5.1  $F_0$  is the amount of time in minutes, equivalent to time at 121°C to which a unit has been exposed during a sterilization cycle. One method of calculating the  $F_0$  is to integrate the time the unit is exposed to heat in terms of equivalent time at 121°C.

13.5.2 The  $D_{\text{value}}$  is the time, in minutes, required to reduce a microbial population by 90 % (one log value) under specified test conditions (for example : fixed temperature, single species, specified medium, etc.). When heat labile products will not withstand excessive heat treatment,  $D_{121}$  value studies of product isolates are necessary to determine the minimum Lethality Factor ( $F_0$ ) that will provide an acceptable assurance of sterilization.

13.5.3 The minimum  $F_0$  value required by a process can be related to the  $D_{\text{value}}$  of the bioburden by the following equation :

$$F_0 = D_{121} \times (\log A - \log B)$$

Where :

$D_{121}$  is equal to the time required at 121°C to reduce the population of the most heat resistant organism in the unit by 90 % ;

"A" is the microbial count per container; and

"B" is the maximum acceptable probability of survival ( $1 \times 10^{-6}$  for pharmaceutical dosage forms) .

13.5.4 Laboratory studies which determine the number and resistance of microorganisms associated with a product (bioburden) serve as the basis for calculating the required minimum  $F_0$  value required for sterilization.

13.5.5 A more conservative approach assumes a  $D_{121}$  value of 1 minute ( $D_{\text{value}}$  of a highly heat resistant spore forming organism such as *Geobacillus stearothermophilus*) for the bioburden of the product.

### 13.6 Heat distribution studies

Heat distribution studies are performed in order to determine temperature variation throughout the sterilizer chamber. These studies should encompass empty chamber and loaded chamber evaluation and should be performed according to written procedures using temperature measuring sensors or probes which have been calibrated before and after use.

13.6.1 The temperature uniformity requirements based on the type of sterilizer and specific processing parameters should be specified.

13.6.2 Empty chamber heat distribution runs must be done during equipment qualification. This should consist of three or more runs using the maximum and minimum cycle times and temperatures specified for the equipment. The studies should demonstrate that the temperature uniformity throughout the empty chamber is within the temperature variation limits established in the protocol.

13.6.3 Multiple temperature probes must be used in each test run. Simultaneous data recording must be available to sense each individual probe at specified time intervals in order to permit determination of the slowest and fastest heating zones in the chamber. The location of each these probes must be documented. These probes must be placed in a manner to adequately demonstrate temperature distribution throughout the sterilizer chamber.

- 590 13.6.4 The data from all runs must be collated into a temperature profile of the chamber.  
591
- 592 13.6.5 Loaded chamber heat distribution studies must also be performed using maximum and minimum  
593 chamber load configurations to represent various products and packaging configurations with  
594 consideration to the following :
- 595
- 596 13.6.5.1 Multiple temperature probes are placed throughout the chamber but not inside the  
597 units of the load to determine the effect of any defined loading pattern on the  
598 temperature distribution within the chamber.  
599
- 600 13.6.5.2 The test runs of a sterilization cycle should be performed using the different container  
601 sizes to be processed using the sterilization parameters specified for the normal  
602 production process.  
603
- 604 13.6.5.3 The position of each temperature probe in each test run must be documented.  
605
- 606 13.6.5.4 The slowest heating point (s) , or cold spot (s) , in each run must be determined and  
607 documented.  
608
- 609 13.6.5.5 A minimum of 3 repeat runs must be performed to establish whether, for a given load  
610 configuration, the location of the cold spot(s) is fixed or variable.  
611
- 612 13.6.5.6 A temperature distribution profile for each chamber load configuration should be  
613 developed and documented.  
614
- 615 13.6.6 It must be demonstrated that all runs of a sterilization cycle consistently meet the specified  
616 criteria for acceptable temperature uniformity.  
617
- 618 13.6.7 Each test run performed must be evaluated. The completed studies should be certified prior to  
619 beginning heat penetration studies.  
620
- 621 13.7 Heat Penetration Studies  
622
- 623 In order to verify that the sterilizing temperature has been reached throughout the load subjected to moist heat  
624 sterilization, it is necessary to conduct heat penetration studies. These studies are conducted to ensure that  
625 the coolest unit within a pre-defined loading pattern (including minimum and maximum loads) will consistently  
626 be exposed to sufficient heat lethality (minimum  $F_0$  value) .  
627
- 628 13.7.1 Heat penetration studies must be performed according to detailed written procedures using  
629 temperature sensing probes which are calibrated before and after use. Simultaneous data  
630 recording must be available to sense each individual temperature probe within specified time  
631 intervals to permit determination of the slowest and fastest heating units in the chamber.  
632
- 633 13.7.2 The validation protocol should make provision for such variables as container size, design,  
634 material, viscosity of solution and fill volume. The container should have the maximum fill  
635 volume of a solution with heating characteristics as slow as the slowest-to-heat solution  
636 sterilized by the specified cycle. Initial container temperature mapping studies should be  
637 considered depending on the container size.  
638
- 639 13.7.3 Heat penetration studies must be conducted with the maximum and minimum loading  
640 configurations for each sterilization cycle using sterilization parameters representative of  
641 normal production cycles.  
642
- 643 13.7.4 Heat delivered to the slowest heating unit of the load is monitored and this data is employed to  
644 compute the minimum lethality ( $F_0$  value) of the sterilization process. Once the slowest  
645 heating units of the load have been identified; at least three replicate runs should be performed  
646 to verify that the desired minimum process  $F_0$  value can be achieved reproducibly

throughout the load. The process is considered acceptable once such consistency in lethality has been adequately established.

#### 13.8 Biological Challenge Reduction Studies

Studies of biological challenge reduction as described in Section 12 are performed.

### 14. Process Validation : Sterilization by irradiation

#### 14.1 Introduction

Radiation processing, in the context of this guide, is considered to mean the exposing of the product to ionizing radiation (for example : such as gamma radiation generated by an isotopic source such as Cobalt 60 radionuclides or Cesium 137 radionuclides, or to an electron or X-ray beams, or the photons generated from an electron beam generator machines) in a controlled manner to ensure that a pre-determined dose is delivered to the product.

Radiation sterilization is used mainly for the sterilization of heat sensitive materials and products. In that many medicinal products and packaging materials are radiation-sensitive, this method is permissible only when the absence of deleterious effects on the material/product has been confirmed prior to use.

#### 14.2 Product Definition and Qualification

The purpose of the product definition is to define the product to be sterilized and to determine its microbiological quality prior to sterilization. Product to be sterilized should include packaging materials. A system should be specified and implemented to ensure the effectiveness of the sterilization process.

14.2.1 A product qualification program demonstrates the effects of ionizing irradiation on the product. The most important outcome of product qualification is the determination of the product's Maximum Tolerated Dose ( $D_{maxT}$ ) for the product. In addition the Maximum Process Dose ( $D_{maxP}$ ) and the Minimum Process Dose ( $D_{minP}$ ) will also be set.

14.2.2 The  $D_{maxT}$  is that dose of radiation which induces an unacceptable change in the analytical profile of the pharmaceutical. It may be possible to select a radiation dose at which no radiation induced changes in the analytical profile can be detected. It is important in the initial product qualification steps to test the product using widely separated radiation doses. This will quickly assess the ability of the product to withstand radiation and to " zero-in " on the most appropriate radiation dose for further testing.

14.2.3 Prior to commencing any determination of  $D_{maxT}$  for the product, it is essential to determine if any of the components of the product have received prior radiation treatment. Radiation effects are cumulative. Therefore, any prior radiation treatment will affect the interpretation of dose-effect experiments. The effects of variations in density of the packages are also a consideration to be looked at.

14.2.4 The  $D_{maxP}$  for a product must not exceed its  $D_{maxT}$ . It is determined by judgment. It is usually set below the  $D_{maxT}$  to ensure that the product is not overexposed. It is dependant upon the product loading, and the physical parameters of the irradiator, such as source strength.

14.2.5 A third factor is the  $D_{minP}$ . The  $D_{minP}$  is determined by the product loading pattern, density, and the operating characteristics of the irradiator. The ratio of the  $D_{maxP}$  to the  $D_{minP}$  is known as the  $D_{max}/D_{min}$  Ratio. This Ratio is the key to successful radiation processing.

#### 14.3 Sterilizing Agent Characteristics

There are significant differences between the two technologies which affect process validation. For instance, gamma radiation delivers a specified dose relatively slowly (over a period of minutes to hours) , to a large

704 volume of product. Conversely, an electron beam generator can deliver the same dose in a fraction of a  
705 second to a very small volume of product. These and other factors make it imperative that a product be  
706 validated independently for each source of radiation.

707  
708 The following has to be defined at minimum :

- 709 - type of radiation to be used in sterilization
- 710 - for electrons or X-rays, the energy level of the electron beam should be specified
- 711 - the potential for induced radioactivity in product should be assessed

#### 712 713 14.4 Process Definition (Sterilization Approach)

714  
715 The purpose of process definition is to establish the maximum acceptable dose and the sterilization dose for  
716 the sterilization process.

717  
718 To establish the maximum acceptable dose, the facility has to be capable of assessing product with regard to  
719 its intended function. The product has to be representative of that to be produced routinely and the source of  
720 radiation has to be capable of precisely delivering required doses.

721  
722 Three basic approaches can be employed to develop a sterilization process for radiation processing : Overkill,  
723 Bioburden-Based, and Species-Based Bioburden Sterilization. Detailed guidance can be found elsewhere (for  
724 example : ISO 11137 parts 1 and 2) .

725  
726 14.4.1 The Overkill method has traditionally been used when the product can withstand radiation doses in  
727 excess of 25 kGy, without adverse effects. It is based on worst-case bioburden assumptions. The  
728 irradiator and product loading parameters are selected to assure that the product receives the  $D_{\min P}$  of  
729 25 kGy and that the  $D_{\max T}$  is not exceeded.

730  
731 14.4.2 The Bioburden-Based approach is well explained and detailed in the ISO Guidelines. In using this  
732 approach, it is necessary to demonstrate that the pharmaceutical product's bioburden is similar in  
733 nature to that assumed for the ISO calculations. This approach is only relevant in cases where the  
734 product's bioburden (before treatment) is consistent, and can be proven to be so. The result is a  
735 treatment dose that is tailored to the actual need (bioburden) , and that is less than the very high (for  
736 pharmaceuticals) 25 kGy.

737  
738 14.4.3 The Species-Specific Bioburden approach is more particularly suited to the pharmaceutical industry as  
739 it relates the radiation dose delivered to the most resistant organism in the bioburden population found  
740 in the manufacturing area. This population should be significantly skewed in the direction of radiation  
741 sensitive organisms, especially when dealing with aseptic processing areas. This should result in a  
742 much lower dose of radiation being needed to achieve sterilization. For this method to be effective it is  
743 necessary to conduct dose distribution studies to determine the product loading pattern which  
744 achieves the best possible  $D_{\max}/D_{\min}$  ratio.

745  
746 14.4.4 Validation studies must confirm that the product in the  $D_{\min}$  position actually receives the minimum  
747 dose, and that the product in the  $D_{\max}$  position does not exceed the ( $D_{\max P}$ ) .

#### 748 749 14.5 Dose Distribution Studies

750  
751 Dose distribution studies are performed in order to determine the  $D_{\max}$  and  $D$  positions in the irradiator  
752 transport mechanism for the product in its predetermined loading configuration; and to confirm that the  
753 radiation dose delivered to the product does not vary outside the process specification.

754  
755 14.5.1 These studies must be performed according to written procedures using appropriately placed  
756 dosimeters which have been calibrated against a known standard.

757  
758 14.5.2 The location of each dosimeter must be documented. The placement of the dosimeters must  
759 ensure that an acceptable distribution is achieved throughout the  
760 transport/irradiation system.

- 761  
762 14.5.3 The dosimeters must be capable of measuring the dose over the desired range.  
763  
764 14.5.4 The data from all runs should be collated into a dose-map profile for each product  
765 transfer/irradiation device.  
766  
767 14.5.5 Dose distribution studies must be performed for each different product loading configuration,  
768 and each product size.  
769  
770 14.5.6 The studies should prove that the dose uniformity requirements, as contained in the process  
771 specification, are consistently achieved.  
772  
773 14.5.7 Failure to demonstrate operational consistency within the chosen criteria for acceptable dose  
774 uniformity precludes the validation of the process. Each test run performed must be evaluated. The  
775 completed studies must be certified.  
776
- 777 14.6 Product Loading Patterns  
778  
779 The configuration of the product in/on the transport mechanism for conveyance through the irradiator is critical  
780 to achieving the specified  $D_{\max}/D$  ratio and the specified doses and the desired SAL. A detailed "map" of how  
781 the product is to be placed in/on the transport mechanism forms a part of the process validation  
782 documentation.  
783
- 784 14.7 "Cycle" Interruptions  
785  
786 14.7.1 For mechanical, safety or operational reasons, the radiation source may need to be turned off during  
787 the course of a "treatment", thus interrupting the sterilization treatment. For those products which are  
788 capable of sustaining microbial growth, it will be necessary to define the maximum length of time  
789 permitted for an interruption in relation to the treatment received at the time of interruption. For  
790 example, for gamma radiation processing; if the interruption occurs before 50 % of the dose has been  
791 delivered, and the interruption is of sufficient length to allow for microbial growth, then a procedure  
792 must be in place to define how the product will be handled; for example : allowed to continue, to  
793 restart, or to reject. Data should be available to support the resumption of interrupted cycles where this  
794 practice occurs. For electron beam processing; it will be necessary to determine if a particular unit was  
795 completely irradiated at the moment of shut down.  
796  
797 14.7.2 For both processes it will be necessary to have the appropriate procedures in place to direct the  
798 operator as to the appropriate person to contact in the event of a "cycle" interruption or a delay in the  
799 commencing/completion of the irradiation "cycle".  
800
- 801 14.8 Temperature Control  
802  
803 14.8.1 For those products which are temperature-sensitive, it will be necessary to document the permitted  
804 temperature range of the product upon arrival at the irradiation facility and the time available for  
805 irradiation before the product temperature rises to the maximum tolerated level. It may be necessary to  
806 provide cooling of the product during the irradiation process. The manner in which this is to be done  
807 must be specified. This type of information will form part of the process validation documentation.  
808  
809
- 810 **15. Process Validation : Sterilization by ethylene oxide and other gases**  
811
- 812 15.1 Introduction  
813  
814 Sterilization by Ethylene Oxide (EtO) is due to alkylation of sulphhydryl, amino, carboxyl, phenolic and hydroxyl  
815 groups in spore and vegetative cells. It also causes a reaction with the nucleic acids of the bacterial cell.  
816

817 Factors that influence sterilization include : bioburden, packaging, package density, product/ package loading  
818 patterns; pre-cycle conditioning, gassing and evacuation times, exposure to relative humidity, exposure  
819 temperature, EtO gas concentration.  
820

## 821 15.2 Product Definition

822

823 Product definition should be performed prior to the introduction of a new or altered product, package or loading  
824 pattern. Product should be designed to allow the penetration of humidity and EtO to the most difficult to  
825 sterilize locations – it should be demonstrated that the sterilization process is effective (for example : through  
826 the use of PCDs) . Packaging should be designed to allow removal of air and penetration of humidity and EtO.  
827 The system should be specified and maintained to ensure that the microbiological quality and cleanliness of  
828 the product presented for sterilization is controlled and does not compromise the effectiveness of the  
829 sterilization process.  
830

831 Primary packaging must be able to tolerate cycle parameters while maintaining product and package/  
832 container integrity for the expected life of the product. Consideration must be given to the influence of EtO  
833 sterilant to the product sterility due to moisture absorption or glycol formation. Inadequate package design may  
834 lead to problems. These problems are caused by use of non-porous materials; attachment of labels with large  
835 surface areas to breathable materials; use of plastic or foam inserts/ supports; application of moisture resistant  
836 coatings.  
837

838 Choice of packaging materials should include consideration of its resistance to chemical and physical changes  
839 during the sterilization process such as : physical strength and permeability. The sterilizing gas must not affect  
840 the product integrity, such as the causing of cracking, phase separation and bio-compatibility. Product design  
841 should avoid resistance of EtO penetration such as use of pressure relief valves, stopcocks, manifolds, cotton  
842 plugs which restrict EtO penetration; application of bleaching agents that contain free chlorine which react with  
843 EtO, Ethylene Chlorhydrate or Ethylene Glycol.  
844

845 Any changes to primary or secondary packaging or in package or case configuration or case composition may  
846 have an impact upon the sterilization of the product and will require evaluation.  
847

## 848 15.3 Sterilizing Agent Characteristics

849

850 Validation should be carried out using a defined sterilizing agent. EtO may be used as a pure gas (100 % ) or  
851 in a mixture of gases such as carbon dioxide or nitrogen. The composition, storage conditions and shelf life for  
852 the sterilizing agent should be specified. Evaluation of the effects of EtO on product should be performed and  
853 documented together with the criteria against which the properties of materials were assessed.  
854

855 During EtO sterilization cycle development and validation studies, biological indicators should be tested as  
856 soon as possible after exposure to the sterilization cycle because microbial inactivation continues after  
857 completion of the sterilization cycle due to the presence of EtO residues.  
858

## 859 15.4 Process Definition – EtO Sterilization Parameters

860

861 Ethylene Oxide Sterilization is influenced by the following major parameters : relative humidity, temperature,  
862 time at exposure and gas concentration. Design of sterilization cycles by EtO must also consider : product  
863 preparation; delivery of the sterilization parameters and removal of the residual sterilizing agents. Aeration may  
864 be performed within the sterilizer or in a separate area or both. Parameters monitored include  
865 vacuum/pressure levels, temperatures, time, steam and gas concentration, air washes and air flow.  
866

867 EtO sterilization process specification should include at least the following :

- 868
- 869 - definition of the preconditioning, exposure, and aeration phases of the sterilization cycle
- 870 - tolerances for the following variables should be established : temperature, humidity, EtO concentration, and  
871 time
- 872 - pretreatment of product to achieve specified temperature and humidity within the load should be performed  
873 under controlled conditions.

- 874 - humidity used for preconditioning and conditioning of product should be generated by steam  
875 means of monitoring and controlling the process variables should be specified.  
876

877 15.4.1 Relative Humidity : Maintaining an appropriate humidity in the sterilization chamber  
878 increases the effectiveness of the EtO sterilization by increasing EtO penetration through cell  
879 walls. A relative humidity of about 35 % is desirable as it has been demonstrated to be  
880 beneficial for effective EtO sterilization. Increased humidity can cause the formation of  
881 condensation on the product, the chamber walls, and optical EtO sensors. Products and  
882 materials sterilized using cycles with relative humidity of less than 30 % are known to have an  
883 increased microbiological resistance.  
884

885 15.4.2 Temperature : EtO cycle effectiveness improves as the temperature increases. The temperature  
886 in the chamber must be high enough to prevent the EtO from liquefying. Product tolerance for  
887 the required high temperatures must be considered.  
888

889 15.4.3 Gas Concentration: at higher EtO levels, the sterilization process is more effective and  
890 requires a shorter dwell time. As the EtO gas concentration increases from 50 to 500 mg/L,  
891 the inactivation rate increases.  
892

893 15.4.4 Diffusion: the higher the diffusion rate of EtO from the chamber to the product in the load the  
894 shorter the required dwell time. Diffusion is improved by creating a vacuum in the chamber  
895 before it is charged with EtO.  
896

897 15.4.5 Time : the exposure of the product at temperature and EtO gas concentration during EtO  
898 exposure.  
899

## 900 15.5 Design of Ethylene Oxide Sterilization Cycles 901

902 The sterilization process to be validated should be specified prior to the introduction of a new or altered  
903 product, package or loading pattern and should be defined to support the validity of process parameters and  
904 their tolerances as defined in the sterilization process specification.  
905

906 There are three traditional approaches in the design of EtO sterilization cycles. Detailed guidance can be found  
907 elsewhere (for example : ISO 11135-1).  
908

909 15.5.1 Overkill cycle : This is the most common cycle. The cycle is developed by performing  
910 fractional cycles to establish the survivor curve with biological indicators and product  
911 samples. The exposure time is then doubled to provide the overkill sterilization process.  
912 Thereafter routine bioburden monitoring should be performed.  
913

914 15.5.2 Biological indicator (BI) /Bioburden cycle : This sterilization process involves the use of a  
915 microbial challenge population lower than  $10^6$ . However, the challenge population should be  
916 not less than  $10^3$ . Bioburden testing is performed to ensure the challenge organism is more  
917 difficult to kill than the bioburden. *Bacillus atrophaeus* is commonly used for the purpose of  
918 EtO sterilization because of its high resistance. The BI should be distributed throughout the  
919 product load and in the same orientation. The placement should include spots that present the greatest  
920 challenge to the sterilization cycle.  
921

922 15.5.3 Absolute Bioburden cycle : This cycle is used when the product bioburden by nature of its location on  
923 the product, the natural resistance, or the population level or any combination of these items may  
924 require the use of absolute product bioburden to monitor the sterilization process because of  
925 resistance. Routine bioburden monitoring is required.  
926

927 Cycle development includes exposing representative samples to incremental exposures and testing  
928 the exposed samples for recovery of survivors and performing counts. The more resistant organisms  
929 are isolated and used in EtO cycle development studies and an inactivation curve is established. The  
930 inoculums should consist of the bioburden average plus three standard deviations ( $3\sigma$ ).  
931

932 15.6 Validation of Ethylene Oxide Sterilization Cycles  
933

934 15.6.1 Validation of EtO sterilization should include Installation Qualification (IQ) , Operational Qualification  
935 (OQ) , and Performance Qualification (PQ) .  
936

937 15.6.2 Each loading configuration should be supported by PQ studies.  
938

939 15.6.3 Microbiological PQ should demonstrate that on application of the sterilization process, the specified  
940 requirements for sterility are met. It is common practice to conduct robustness studies by altering one  
941 or more process variables, for example : EtO concentration, temperature, humidity compared to the set  
942 points used in routine sterilization (below or at minimum levels specified for routine control) .  
943

944 15.6.4 Lethality of the cycle should be determined using BI, Overkill or Absolute Bioburden approach.  
945

946 15.6.5 Physical PQ should demonstrate reproducibility of the process and should include a minimum of three  
947 consecutive successful runs where specified acceptance criteria are met throughout the load for the  
948 duration of the proposed routine process specification.  
949

950 The following are additional consideration to be made in the Validation of an EtO Sterilization Cycle.  
951

952 15.6.5.1 Determination of rates of dissipation of the three major residues after being subjected  
953 to the EtO sterilization cycle.  
954

955 15.6.5.2 The maximum allowable levels of EtO residues on drug products must be specified.  
956 These limits must be based on safety studies and on published international safety  
957 standard. Provisions for the routine monitoring of the levels of EtO, ethylene  
958 chlorohydrin (ECH), and ethylene glycol (EG) on drugs, drug products, and biological  
959 products must be in place.  
960

961 15.6.5.3 Validated analytical methods for the determination of EtO, ECH and EG residues  
962

963 15.6.5.4 Validation of gaseous sterilization procedures should involve additional considerations  
964 such as determination of time and humidity in the preconditioning area, temperature,  
965 pressure, time and humidity in the chamber, ventilation of load after sterilization, the  
966 method used to recover the challenge spore, the incubation period of the exposed  
967 spores.  
968

969 15.7 Sterilization With Vapor Phase Hydrogen Peroxide (VHP)  
970

971 VHP is used mainly in surface sterilization such as in flexible and rigid isolators, pass-throughs, production  
972 filling lines, biological safety cabinets and clean rooms. Its use in terminal sterilization of pharmaceutical  
973 dosage forms is very limited.  
974

975  
976 **16. Post validation process monitoring**  
977

978 The sterilization process must be monitored routinely to ensure that the process conditions are routinely met as  
979 specified. These results should be documented in the processing records.  
980

981 16.1. The requirement for, the existence of, and adherence to effective, routine process-monitoring  
982 procedures should be included in the validation protocol.  
983

984 16.2 Biological challenges should be documented when performed in routine process monitoring  
985 procedures. The location, number, type and lot number of the challenge must be included in the  
986 records along with the actual test results.  
987  
988  
989

990 16.3 Deviations from defined processing conditions must be documented, investigated and assessed  
991 regarding the impact on the product, and on process objectives. In the absence of qualified  
992 evaluators, the sterilization process should automatically be considered to have been compromised.  
993

994 For sterilization approaches based on either of the two Bioburden-Based methods (Irradiation-14.4.2 and EtO-  
995 15.5.3), samples for ongoing bioburden testing and data collection should be obtained from each batch of drug product  
996 for an initial period of time sufficient to define the limits of species and number of organisms for seasonal/operational  
997 variations to be adequately documented and controlled.  
998  
999

## 1000 **17. Requalification and Reevaluation**

1001  
1002 The validation and validity of the process are verified at scheduled intervals, at least annually. All changes to the  
1003 equipment, sterilization system, sterilization or process parameters, and primary packaging components must be pre-  
1004 authorized through the Change Control Procedure or be required as part of a pre-established maintenance program.  
1005 Re-validation is carried out whenever significant modifications or changes are made.  
1006

## Appendix A

### Glossary of Terms

The following definitions supplement the definitions provided under the Glossary of Terms in the “GMP Guidelines (GUI-0001)”.

**Bioburden** - The total number of viable microorganisms on or in a pharmaceutical product or in the manufacturing environment prior to sterilization processing.

**Biological Indicator (BI)** - A characterized preparation consisting of a number of microorganisms (bacterial spores) of known resistance to the sterilization method to monitor adequacy of sterilization.

**Chemical Indicator** (non-biological indicator) - Test system that reveals change in one or more pre-defined process variables based on a chemical or physical change resulting from exposure to a process.

**D<sub>VALUE</sub>** - The decimal reduction time/dose or time required to reduce a microbial population by 90% (one log value) under specified test conditions.

**D<sub>maxT</sub>** - The maximum dose tolerated by the product before product degradants increase to significant levels. (Sterilization by Irradiation)

**D<sub>maxP</sub>** - The maximum process dose allowed. This dose is product dependent or determined on a case by case basis. It is set below the D<sub>maxT</sub>, to prevent damage to the product, but is high enough to ensure that the D<sub>minP</sub> will achieve the desired SAL. (Sterilization by Irradiation)

**D<sub>minP</sub>** - The minimum process dose. This dose is determined by the configuration of the irradiation facility and the loading pattern/density of the product. (Sterilization by Irradiation)

**D<sub>121</sub>** - D value of the BI at an exposure temperature of 121°C. (Sterilization by Moist Heat)

**F<sub>0</sub>** - The amount of time in minutes, equivalent to time at 121°C, to which a unit has been exposed during a sterilization cycle. (Sterilization by Moist Heat)

**kGy** - The Gray (Gy) is the international unit for measuring the radiation dose delivered. 1 kGy=100,000 rads or 0.1 MRad (old terminology).

**Process Challenge Device (PCD)** - Item designed to constitute a defined resistance to a sterilization process and used to assess performance of the process.

**Sterility Assurance Level (SAL)** - Expected probability of a surviving microorganism on each individual product after exposure to a valid sterilization process.