[Explanation: Delete. With respect to the bioburden method, a company needs to be using an appropriate validated method. Requiring firms to evaluate new technology cannot be a GMP requirement or a requirement in a NOTE FOR GUIDANCE. Whether the company has the resources to provide evidence that alternate methods have been evaluated should have no bearing on the appropriateness of the in-use method or on whether the company can/cannot be approved for parametric release. The pharmaceutical industry strongly relies on pharmacopoeial methods. Using other methods needs intensive validation to show comparability with established methods. This chapter obviously mandates for the use of non-pharmacopoeial "new" methods. If the actual pharmacopoeial methods are considered to be not sufficient anymore, these should be updated, rather than putting vague demands in this guideline.]

~~7.5.6 For aqueous or otherwise microbiologically unstable products the time lag between dissolving the chemical starting materials, product fluid filtration and sterilization should be examined. These time lags should be set to minimise the development of pyrogens (if applicable) and bioburden.~~

[Explanation: Delete. While this is an example of properly written GMP requirement, it is state of technology to control the holding time of parenterals prior to filling and not specific to parametric release.]

~~7.5.7 The microbiological state of the container and closure should be controlled and meet limits based on sound micro biological rationale.~~

[Explanation: Delete. Routine in-process and product integrity testing is not done in practice after each sterilization load. Data for container closure integrity showing maintenance of sterility are gathered during product development and supplied in the product submission package (see 7.4.2).]

~~7.5.8 The microbiological state of the fluid contact parts of the filling system should be controlled. Note that this may include the following:~~

~~(a) Gases.~~
~~(b) Solvents.~~
~~(c) Lubricating fluids.~~
~~(d) Details of pipework.~~
~~(e) So called hygienic connecting joints.~~
~~(f) Welds.~~
~~(g) Internal structure of valves, turbine fillers etc.~~

[Explanation: Delete entire section. This section deals in excess detail with the filling system. This may be appropriate for aseptic processing but not for parametric release of products sterilized in their final container by a validated cycle.

Testing of gases, solvents, lubrication fluids, where appropriate, should be done during validation and should be addressed in the validation plan. Routine testing seems superfluous, if validation was performed properly.]

7.5.9 The following elements should be *considered in the risk assessment* ~~carefully reviewed~~ as they *may be* ~~are often~~ involved in loss of control of bioburden:

(a) Design.
(b) Cleaning.
(c) Sanitization.
(d) Microbiological monitoring.
(e) Planned preventative maintenance.
(f) Breakdown repair.
(g) Change contol and validation.
(h) Operator error or non compliance with procedure.

[Explanation: Clarification.]

~~7.5.10 With regard to the product filter the following should be reviewed:~~

~~(a) The grade of product filter.~~
~~(b) The effect of product on the filter.~~

~~(c)Its initial microbiological condition.~~
~~(d)Its period of use.~~
~~(e)Whether it is washed, sterilized, and reused (a practice to be discouraged).~~
~~(f) The method of integrity testing, off line or on line.~~
~~(g) Storage in between.~~
~~(h) At which stage in the process it is integrity tested.~~
~~(i) What decisions are taken if it fails the test.~~
~~(j) The micro biological state of the test equipment.~~
~~(k) Microbiological monitoring of product fluid after the filter.~~
~~(l) Method of sampling and holding conditions.~~

[Explanation: Delete or modify. This section gives unreasonable emphasis on the filtration process while trying to provide guidelines for terminal sterilization. While filtration is used to reduce bioburden the requirements formulated in the draft would be appropriate for sterilising filtration in aseptic manufacturing processes. This is not appropriate for terminal sterilization processes.]

7.5.11 At lower priority, from the point of view of the sterility assurance system, are the details of environmental control of the filling area and the associated monitoring and the details of microbial control of stages prior to filtration. ~~These areas still need review for pyrogen control and general aspects of GMP.~~

[Explanation: Delete last sentence. Pyrogen requirement is not properly addressed in this section. It is broadly but unreasonably applied to all aspects of EC monitoring in this section. General aspects of GMP should be addressed in Annex I where needed.]

~~7.5.12 In the event of the loss of control of presterilization bioburden particularly if this is due to a type of micro-organism resistant to the sterilization process clues as to the root cause of the problem may be found in parallel loss of control in these more peripheral areas.~~

[Explanation: Delete. The meaning of this paragraph is cryptic. Control in bioburden in a general GMP question and not specific to parametric release.]

~~7.5.13 There should be evidence of some level of monitoring and, if possible, control further back into the chain. This should extend to monitoring chemical starting materials particularly for the presence of microorganisms that may be resistant to the sterilizing agent. As an example, if a chemical is contaminated with heat resistant bacterial spores the mixing area will become contaminated and it is only a matter of time before cross contamination or a weakness in one of the control systems results in contaminated product and a challenge to the sterilization process.~~

[Explanation: Delete. This paragraph indicates a basic lack of understanding of microbiological selection principles. Resistance of micro-organisms against a sterilization principle does not offer a selective advantage for survival and multiplication in the production environment. Monitoring the area and bioburden for resistant bacterial endospores is a basic GMP requirement and not connected to parametric release.]

7.5.14 The way in which monitoring limits are set and acted upon and the consideration of the need for trend analysis should be documented with a valid rationale.

[Explanation: Items 7.5.11 and 7.5.14 seem to give confusing and contradictory messages, e.g., "Environmental control is a lower priority," "is important in understanding loss of bioburden control of the product," "Evidence of monitoring back into the chain." The text must be consistent, e.g., there should be an adequate level of environmental monitoring to demonstrate control of the manufacturing environment. There should be a programme for sampling and testing chemical raw materials.]

7.6 Sterilization process

7.6.1 Only terminal sterilization processes ~~that incorporate large safety margins~~ will be considered. This should not result in a relaxation of attention and the rigour of steriliser and service design, maintenance, operation and validation should be of ~~the highest~~ *appropriate* quality.

[Explanation: Clarification. Vague statements like "that incorporate large safety margins" are not science-based decisions. If it is the position that only overkill processes like the European Pharmacopoeia Standard Process can be considered for parametric release, this should be clearly stated and sould be further discussed. However, it is the position of the industry that a sterility assurance level (SAL) of 10^{-6} as required by the Pharmacopoeias worldwide and which cannot be guaranteed by sterility testing but only by validation, is sufficient. Sterility testing does not contribute to the SAL so there is no reason why omission of this test should require sterilization processes which provide a higher SAL.]

7.6.2 Any process to be considered for elimination of routine sterility testing should be adequately validated initially and revalidated on a routine basis. The validation should demonstrate that a specified sterility assurance level (SAL) can be achieved throughout the load.

7.6.3 Routine monitoring of the process should demonstrate that the validated conditions necessary to achieve the specified SAL are achieved in each cycle.

7.6.4 The degree of micro biological inactivation delivered by the cycle used routinely should be estimated and shown to provide a Sterility Assurance Level *of at least* 10^{-6} ~~–.better than Pharmacopoeial recommendations~~.

[Explanation: Sterility testing does not contribute to the SAL, therefore, there is no reason why omission of this test should require sterilization processes which provide a higher SAL (see 7.6.1). The requirement to provide a SAL better that Pharmacopoeial expectations is not a science driven expectation and is in conflict with the European Pharmacopoeia.]

~~7.6.5 The expectation of detailed system analysis to discover all failure modes discussed in the **Overall considerations** section above is particularly relevant to steriliser~~s~~. Each step of the often complex cycles should be known, the ways in which the step could deviate, the effect of this, and the ways in which the deviation could be detected or better, designed out, should all be available for inspection.~~

[Explanation: Delete as this is a redundant statement. See comments on FMEA and HACCP.]

7.6.6 The loads validated should be precisely defined including position of product on the truck or carrier, position of carrier in the steriliser and should reflect loads routinely processed.

7.6.7 The validation studies should demonstrate that the sterilizing agent is homogenous or follows a predictable pattern inside the chamber.

~~7.6.8 Penetration of the sterilizing agent throughout all the necessary parts of the product should be demonstrated directly.~~

[Explanation: In many cases in pharmaceutical sterilization, closed containers are not penetrated by the sterilising agent.]

~~7.6.9 Where there is no alternative, for example in micro environments inside the product, biological indicators may have to be used, but this may raise questions about how robust the validation is.~~

[Explanation: Meaning of the paragraph is unclear. Bioindicators are used widely in the industry as the only possible means to directly validate process lethality. The suggestion that the use of biological indicators puts in doubt the effectiveness of the validation is inappropriate and inconsistent with decades of industry experience.]

7.6.10 Appropriate steriliser validation guidelines should have been consulted and the details of validation should have a properly documented rationale. ~~For irradiation process EN 552: 1994 "Sterilization of Medical devices -Validation and routine sterilization by irradiation" may be applicable.~~

[Explanation: The scope of the document is medicinal products for human and veterinary use. Referencing a standard for medial devices seems unusual. It is for a company to provide the rationale for the approach to be taken irrespective of the references used.]

7.6.11 The derivation of the specification for the cycle to be used routinely from the load qualification studies part of the validation should include the rationale for the selection of the allowed tolerances of the parameters that define the sterilization process.

7.6.12 The cooling phase of a heat based cycle should not offer any opportunities for recontamination of product that may transiently have lost integrity i.e. the cooling medium should *meet the microbiological requirements of WFI.* ~~be sterile.~~

[Explanation: The USP has a limit of 10cfu/100 ml for cooling water. Sterility is an inappropriate requirement as this cannot routinely be tested without the use of a sterility test. Is it intended to introduce a sterility test in order to abolish a sterility test? The requirement that cooling medium should be sterile would prevent Parametric Release rather than enable it due to remodeling measures on existing autoclaves and to microbiological considerations].

7.6.13 The programme of revalidation should be *done annually* ~~of sufficient frequency and be adhered to.~~

[Explanation: The statement concerning the revalidation programme should be more specific.]

7.6.14 The principles of steriliser validation ~~for review during the inspection~~ include the following, but the list is not exhaustive:

[Explanation: It is recommended that the text be incorporated into 7.6.10 (without the reference. It is unclear why this is under revalidation.]

~~(a)The~~ steriliser ~~should be in exactly the same mechanical, electrical and software state as it was during the last validation.~~ *A change control system should be in place.*

[Explanation: In practice, it is impossible to keep any steriliser in "exactly the same mechanical, electrical and software state as it was during the last validation." Emphasis should be paid on proper change control procedures to document and evaluate any performed change with respect to sterility assurance.]

- This focuses attention on the drawings and specifications defining that state and the change control system.
- The planned change control should be approved by both the sterility assurance engineer and microbiologist.
- Unplanned repairs should also be subject to the same level of review and approval prior to being carried out or reviewed sufficiently soon afterwards to prevent possibly compromised product being released.
- The assumptions that 'like for like' replacements are truly 'like for like' and do not require confirmatory testing are often worth challenging.

(b) Routine planned preventative maintenance programmes should have documented completion *according to schedule.* ~~by the programmed date.~~

[Explanation: Typically, manufacturers have time frames not specific dates.]

~~(c)~~ Steriliser ~~and services start up checks should be confirmed as having been carried out successfully prior to sterilizing product each day.~~

[Explanation: This is not specific to parametric release. Where start up checks are required for autoclave performance (e.g., non-condensable gasses, chamber leak test, etc.) this needs to be fixed in a specific SOP. In this case, it is general GMP to follow these procedures.]

(d)The state of the services should similarly be as in the validation. For example the steam pressure and volume available can have an effect on the heat up time so this should be a constant controlled service.

(e)The instrumentation in routine use should be sufficient to confirm the delivery of the validated cycle so it should be independent of the control system instrumentation.

(f)The routine sensing probes should be numerous enough to sample the space or product, be in the same position as for the validation and be calibrated.

(g)The accuracy of standards used to calibrate process measurement instruments should be specified and the calibration should be traceable to national standards.

[Explanation: These are necessary for each validated sterilization cycle and are not specific to parametric release.]

7.7 The segregation of non-sterile product from sterilized product

7.7.1 A gross failure of the sterility assurance system that may be detected by the sterility test is a mix up where product appears in the final packing area or, in the case of sterilization by contractor is sent to the customer or finished goods storage without having been subjected to the sterilization process. It follows that pProduct that has not been exposed to the sterilization process must be rigorously segregated from the flow of product coming out of the steriliser and moving to the next stage in the process.

[Explanation: Guidance on segregation is basic GMP. The deleted text represents the continued search for a reason to justify the sterility test.]

7.7.2 In order to prevent this type of mix up product should not be able to move to the stage of processing following sterilization without passing through the steriliser and having been confirmed as having been exposed to a valid cycle. The following arrangements to prevent this should be inspected:

(a)Physical barriers that ensure entry to the steriliser should be used. These may be quite complex and comprise metal fencing, one way gates, swinging barriers, overhead trackways with controlled points like railway tracks, and carefully positioned posts to prevent carriers turning at cross over regions. The objective of these barriers is to prevent non sterile product entering the flow of sterile product. Such barriers are best used in conjunction with double ended steriliser**s** although well designed swinging barriers or other arrangements can secure a steriliser with only one door.

(b)Well designed and validated electronic systems may provide a substitute for physical barriers. Such systems would be GMP critical and would require an independent second system to confirm the correct functioning of the primary system.

(c)Both physical and electronic systems should be supported by comprehensive contingency procedures to control breakdown situations of even the most minor type. Each failure mode should have a clear method of securing product already in the system defined together with all the necessary steps to correct the problem.

(d)The main flow of product may be secured by these means, but there are other streams of product that may escape control. The obvious ones are samples that may be inadvertently returned to the batch, such as presterilization bioburden samples and samples for marketing purposes. Rigorous tracking and reconciliation is essential for all samples removed from the batch. Rework may also be another product flow that presents a risk. The company's analysis of failure modes and risks should clearly address these issues.

(e)In assessing all these systems it should be born in mind that deliberate attempts to defeat them cannot always be anticipated and neutralised. The company should still take into account the human element and be able to show that risks of human error have been considered and that the motivation to avoid a control system, for example by the presence of an easier pathway, is designed out as far as possible.

(f)On completion of the sterilization cycle the checks carried out by the operator before moving the load out of the steriliser should be as comprehensive as possible to assure that the validated process has been delivered. The steps to be taken if the cycle is not correct should be clearly defined i.e. resterilize if this is

~~validated or move to secure quarantine, and should avoid taking the load out of the~~ steriliser ~~on the sterile side of the barrier system.~~

[Explanation: This section is far too detailed and does not represent guidance specifie to parametric release. Also, (d) implies that a sterility test is an effective means of detecting even small numbers of samples inadvertently returned to the batch, which is not the case.]

7.8 The process of sterility assurance release

7.8.1 The following sterility assurance related items should be confirmed at the appropriate level of authority prior to release of each batch of product.

(a) Details of product integrity and compliance to specification.
(b) All presterilization micro biological release criteria have been met. These should include presterilization bioburden in limits with no signs of adverse trends or associated batches out of limits. All other microbiological indicators should show a process in control.
(c) If applicable, filter integrity test data passes.
(d) The steriliser used had completed all planned maintenance and routine checks
(e) There were no unplanned repairs or modifications that have not been reviewed and released by the sterility assurance engineer, and microbiologist.
(f) All instrumentation was in calibration,
(g) The steriliser was qualified for the product load processed.
~~(h)~~ The number of units of product produced, the number of units of product presented for sterilization, the number of units of product placed into the steriliser and removed on the sterile side of the steriliser, the number of units of product presented to subsequent stages and the number of units of product being considered for release are reconciled.

[Explanation: This section mixes validation data and process monitoring data as well as maintenance records with release data which have to be met lot by lot. With the use of overkill processes, bioburden data may be useful tools to keep the process under control, but a limit excursion does not necessarily have a bearing on final product sterility. This needs to be considered for each process. While validation and change control procedures have to be in place, review of these data is not a topic for batch release.]

7.8.2 The sterilization cycle records should have been reviewed and released by ~~production personnel~~ *Quality Assurance*..

[Explanation: Batch record review is not the responsibility of production personnel.]

7.8.3 The way in which the steriliser load is *identified should result in documentation that clearly provide a record of the exposure to heat of each carrier or the product itself.* labelled should result in documents that clearly provide a record of each carrier of product with a corresponding activated process indicator (such as autoclave tape that has shown exposure to heat).

[Explanation: Clarification.]

7.8.4 Elimination of routine sterility testing may have been authorised subject to the use of more sophisticated process monitors such as thermochemical indicators which degrade in a way that demonstrates that a full process has been delivered. In this case, records of their testing in clear association with corresponding cages trucks or other product carriers should be present.

7.8.5 It should be confirmed that the sterilization cycle that will be used to release the product was started within the bioburden control time constraints, for example the filtration to sterilization time.

~~7.8.6 The~~ sterilization ~~cycle records comply with specification~~

[Explanation: This is necessary for each validated sterilization cycle and not specific to parametric release.]

7.8.7 In the event of an atypical cycle release is approved by the sterility assurance

engineer and microbiologist. Product should only be released if the cycle parameters are within tolerances that were accepted during the validation and in compliance with written procedures.

~~7.8.8 When release involves computer systems all relevant aspects of Annex 11 of the EC Guide to GMP and current good practice should be addressed.~~

[Explanation: This is necessary for each validated sterilization cycle and not specific to parametric release.]

7.9 Inspection when elimination of routine sterility testing has previously been authorised

7.9.1 In addition to confirming continued operation of the approved system particular attention should be given to the company's handling of out of limit or other atypical situations. ~~It is recognised that the desire to maintain the advantages of the elimination of routine sterility testing may place stress on those responsible for assessing the significance of atypical situations.~~ The process of assessing product or process deviations should be based on the facts and on sound objective decisions. This process should be documented.

[Explanation: The aim of the inspection should be to establish that the systems in place are validated and applied in a consistent way. Comments about people being under stress is not a parametric release issue.]

7.9.2 It would also be appropriate to review the rigour with which the company's self inspection programme is adhered to, the qualifications of the auditors and that the scope of the self inspections include all areas related to sterility assurance.

~~8. APPENDIX II~~

~~DETAILED GUIDANCE CONCERNING THE REDUCTION OR ELIMINATION OF OTHER FINISHED PRODUCT, STARTING MATERIALS AND IN-PROCESS TESTING~~

~~8.1 General~~

~~8.1.1 The general basis upon which authorisation may be granted should include the following.~~

~~(a) The demonstration that the test is redundant, i.e. it has not detected any out of alert limit situations, failures or other anomalies not already detected by the remaining system.~~
~~(b) The product quality being assessed is assured, or directly tested by the remaining system.~~

~~8.2 Specific considerations~~

~~8.2.1 When the test in question is being made redundant due to adequate testing elsewhere in the system, the company should provide the following.~~

~~(a) Relevant process validation.~~
~~(b) A concise analysis of the production process showing that any events that could be reasonably predicted, near misses drawn from history and expert risk analysis relevant to the quality being tested for are prevented or their occurrence detected.~~

~~8.2.2 For reduced testing of starting materials all relevant elements of the Guide to GMP must be properly addressed and particular emphasis placed on the following:~~

~~(a) Audit of the manufacturer with rigorous criteria of acceptance. The audit should determine whether the in-process control and testing provide adequate assurance for reduced testing. Repeat audits at least every two years are expected. Suitable third party audits may be acceptable if the reports are reviewed.~~
~~(b) The history of testing of at least three batches with no discrepancies.~~
~~(c) Detailed review of the manufacturer's Certificate of Analysis produced in~~

~~a satisfactory format.~~

~~(d) When starting materials are purchased through agents or clearing houses it is unlikely that the control and knowledge of the whole chain of supply would justify reduced testing.~~

~~8.2.3 If reduced testing is being sought based solely upon the assurance provided by the process then the case should clearly demonstrate that the output of instruments or other data demonstrates unequivocally that the validated process has been delivered.~~

[Explanation: Extension of parametric release to other cases than sterility testing, if needed, should be addressed by a separate specific guideline case by case. (See General Explanation at the beginning of the document]

-- End of PDA Comments --

資料 3

Traditional and Rational Methods for Terminal Moist Heat Sterilization

The following text and figures are provided for rationalizing F_o requirements for terminal moist heat sterilization of pharmaceutical products. While any of these alternative methods could be used to assure sterile products, they are being offered here only as alternatives for products which are adversely affected by the reference conditions suggested in the Pharmacopoeia, namely 15 minutes at 121°C. These alternative methods may be appropriate for products (to include solution, container or packaging) which experience slight, moderate or severe effects following exposure to the above reference conditions for moist heat sterilization. These methods which employ reduced thermal processing or equivalent minutes at 121°C (F_o) would not be possible without appropriate attention to the challenge presented by the bioburden. Each of the alternative methods and requisite bioburden testing are summarized in Table 1 and the associated inactivation shown in Figure 1. The following paragraphs discuss rational methods for terminal moist heat sterilization, which should be investigated prior to using aseptic processing for pharmaceutical products.

Rational Method 1

For products, which exhibit "slight" adverse effects from exposure to moist heat sterilization for 15 minutes at 121°C, Rational Method 1 is suggested. Rational Method 1 requires at least the equivalent of 12 minutes at 121°C ($F_o = 12$), and is capable of inactivating 12 logs of a highly resistant organism such as one which has a D-value of 1 minute. Therefore, if the product were initially contaminated with 1,000,000 organisms of this resistance, the resulting probability of a surviving organism would be one in a million.

Alternatively, the process would be capable of inactivating 8 logs of bioburden, which had a resistance equal to that of the compendial biological indicator *(B. stearothermophilus)* with a D-value of 1.5 minutes. So if 100 such organisms were present in the product, the resulting probability of a surviving organism would be one in a million. This example is included in Table 1 and Figure 1. It is recommended that when using this method that routine, frequent enumeration of bioburden be performed to assure the resistant portion of the bioburden population is not exceeding 100 organisms.

Additionally, this method could be microbiologically validated by a 6 spore log reduction (SLR) of a biological indicator (BI) with a D-value of 2 minutes, a 4 SLR of a BI with a D-value of 3 minutes or a 3 SLR of a BI with a D-value of 4 minutes.

Rational Method 2a

For products, which exhibit "moderate" adverse effects from exposure to moist heat sterilization for the equivalent of 15 minutes at 121°C, Rational Method 2a is suggested. Rational Method 2a requires at least the equivalent of 8 minutes at 121°C ($F_o = 8$), and is capable of inactivating 8 logs of a highly resistant organism such as one which has a D-value of 1 minute. Therefore, if the product were initially contaminated with 100

organisms of this resistance, the probability of a surviving organism would be one in a million. This example is also shown in Table 1 and Figure 1. However, since the resistance of the bioburden is assumed to be less than that of the BI, it is suggested that in addition to the enumeration of bioburden for each batch, that screening of resistance be performed as well to assure the actual resistance is less than or equal to 1 minute.

This method can also be microbiologically validated by, for example, a 4 SLR of a BI with a D-value of 2 minutes or a 2 SLR of a BI with a D-value of 4 minutes. See also alternative biological indicators below.

Rational Method 2b

For products, which exhibit "severe" adverse effects from exposure to moist heat sterilization for the equivalent of 15 minutes at 121°C, Rational Method 2b is suggested. Rational Method 2b is similar to 2a, except that it requires only 4 minutes at 121°C (F_o = 4), and is capable of inactivating 8 logs of a moderately resistant organism such as one with a D-value of 0.5 minutes. Therefore, if the product were initially contaminated with 100 organisms of this resistance, the probability of a surviving organism would be one in a million. This example is also shown in Table 1 and Figure 1. Like the Rational Method 2a, both enumeration of bioburden and resistance screening are suggested for each batch. In this case, the actual resistance of the bioburden must be less than or equal to 0.5 minutes.

Like the other methods, Rational Method 2b can also be microbiologically validated by a 2 SLR of a BI with a D-value of 2 minutes. An alternative biological indicator with a resistance less than that of *B. stearothermophilus* may be more appropriate here in order to better characterize the inactivation rate, and to more appropriately model the resistance of the naturally occuring bioburden. While no guidance is offered with respect to an alternative species, a 4 SLR of a BI with a D-value of 1 minute, or a 5 SLR of a BI with a D-value of 0.8 minutes should be considered.

Aseptic Processing

If the above Rational Methods still result in adverse effects on the product, aseptic processing is acceptable in lieu of terminal sterilization (see also Figure 2).

TABLE 1

Summary of

Traditional and Rational Methods

for Terminal Moist Heat Sterilization

Method Name	Min. F_o	Resistant Population	Maximum Resistance	Bioburden Monitoring		
				Total Count	Spore Count	Resistance Screen
Traditional Method	15	10^4	1.5 min. (assumed)	Periodic	Periodic	Not Applicable
Rational Method 1	12	10^2	1.5 min. (assumed)	Routine Frequent	Routine Frequent	Not Applicable
Rational Method 2A	8	10^2	1.0 min.	Each Batch	Each Batch	Each Batch
Rational Method 2B	4	10^2	0.5 min.	Each Batch	Each Batch	Each Batch

Flowchart for the Traditional & Rational Methods

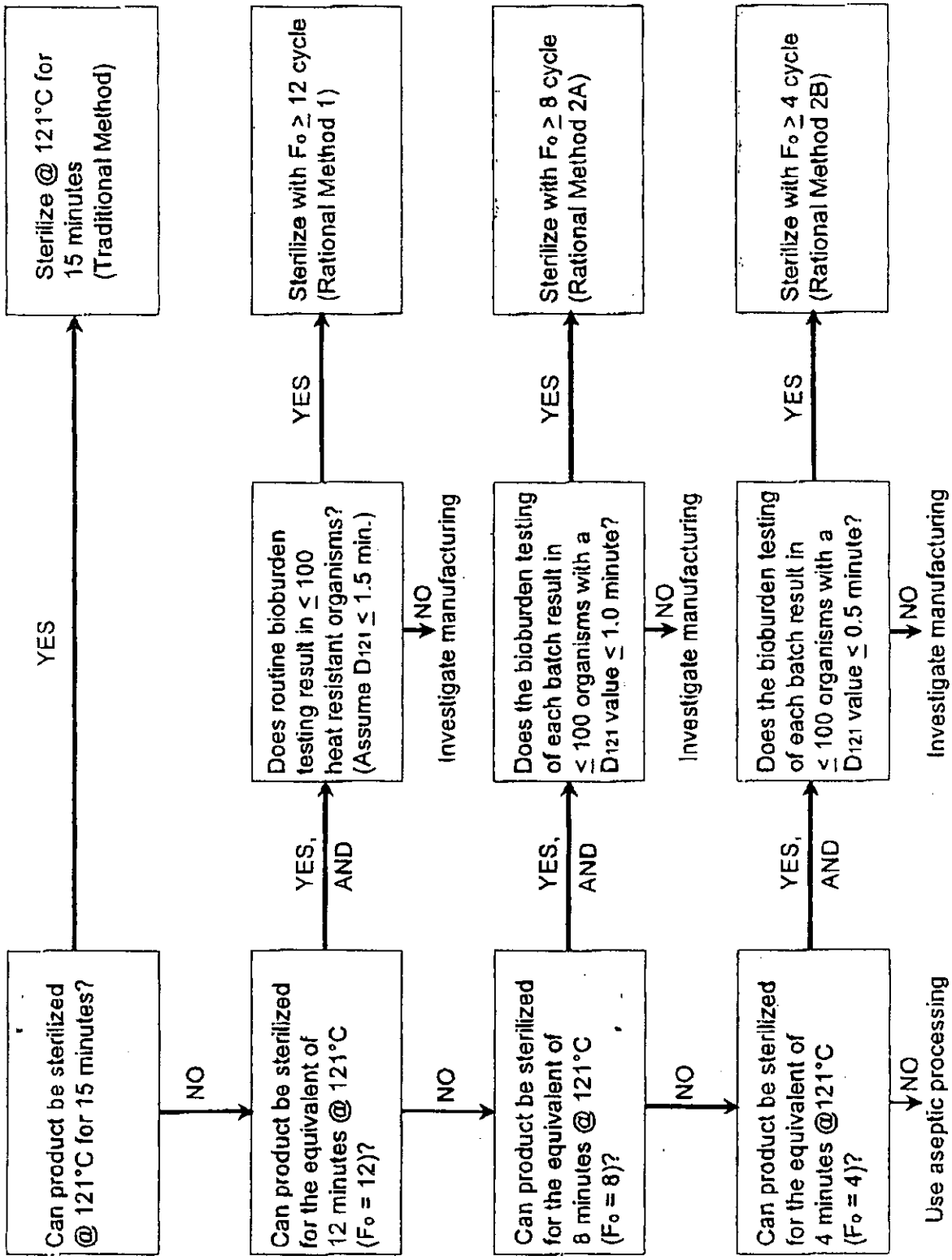

Figure 2

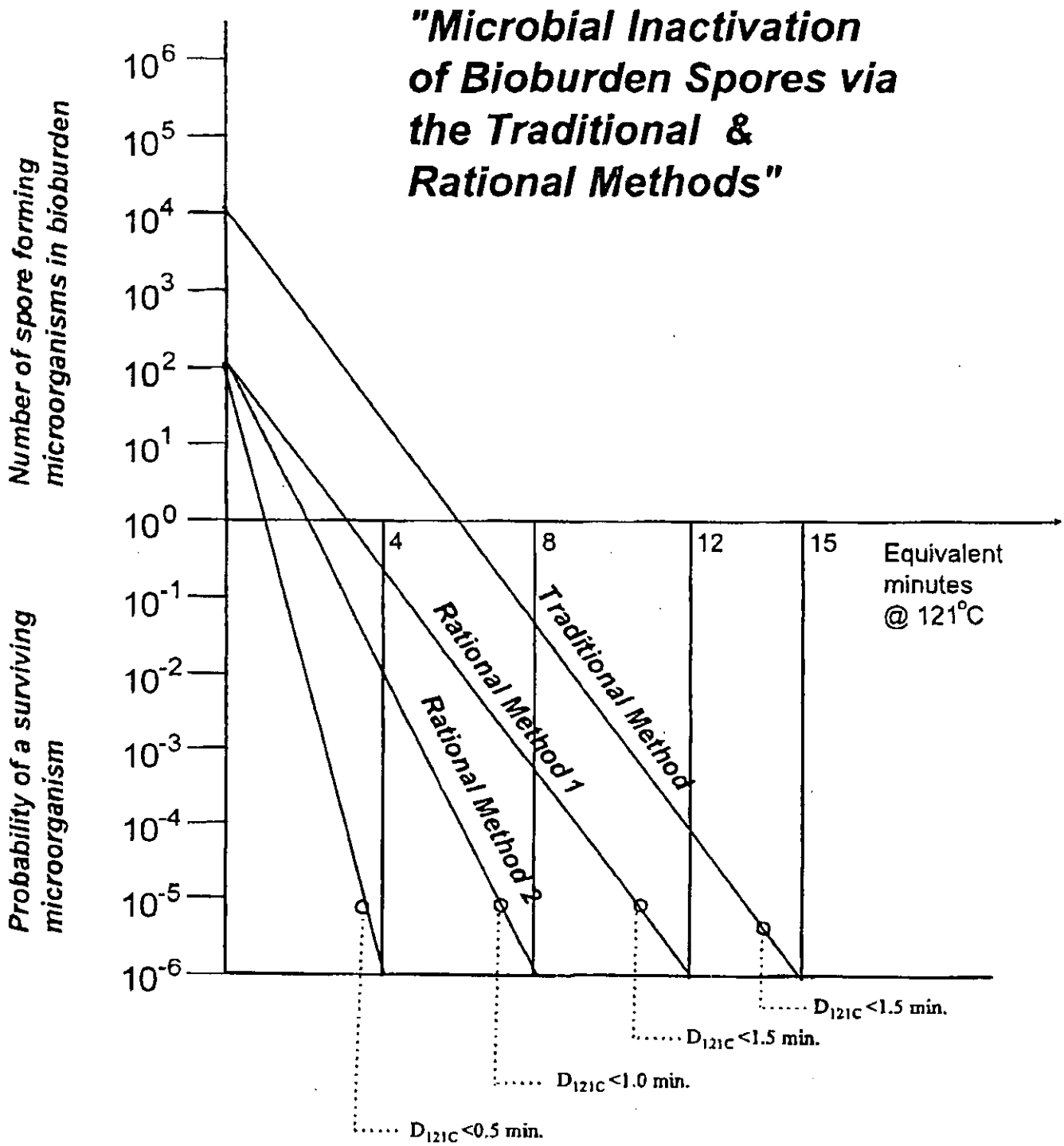
"Microbial Inactivation of Bioburden Spores via the Traditional & Rational Methods"
Number of spore forming microorganisms in bioburden
Probability of a surviving microorganism
10^6
10^5
10^4
10^3
10^2
10^1
10^0
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
10^{-6}
4
8
12
15
Equivalent minutes @ 121°C
Traditional Method
Rational Method 1
Rational Method 2
D_{121C} <1.5 min.
D_{121C} <1.5 min.
D_{121C} <1.0 min.
D_{121C} <0.5 min.

FIGURE 1

資料4

高圧蒸気滅菌医薬品に対するパラメトリックリリース指針案

本指針は、高圧蒸気滅菌医薬品に無菌試験を実施せず、滅菌工程の重要管理項目を適正に管理することによって製品を出荷させるパラメトリックリリースに必要な事項を示す。パラメトリックリリースとは、滅菌機構が十分に解明されており、その重要管理項目も明らかで、適切なバイオロジカルインジケーターを用いてその滅菌工程を微生物学的にバリデートできるときに適用できる方法である。高圧蒸気滅菌法を適用しようとする医薬品については、予め滅菌前後における当該医薬品の安定性（生物学的同等性）及び使用容器の完全気密性を十分に検証しなければならない。その上で、日本薬局方「最終滅菌医薬品の無菌性保証」に示す方法で、滅菌バリデーションを行い、パラメータ管理のみで 10^{-6} 以下の一定の無菌性保証水準が恒常的に得られることを確認できたならパラメトリックリリースの導入を考える。パラメトリックリリース導入後は、無菌試験での出荷はできない。

用語の定義：下記の他、日本薬局方の「最終滅菌法及び滅菌指標体」並びに「最終滅菌医薬品の無菌性保証」による。

1.1　最大バイオバーデン数：広範なバイオバーデン調査によって得られた平均バイオバーデン数に3倍の標準偏差を加えたもの。

1.2　F_0 値

D 値を 10 倍変化させる温度変化の度数として定義される Z 値を 10℃と仮定し，全加熱工程の致死係数（L）を積分して得られた滅菌熱量を T_b における換算時間（分）で表わしたもの.

$$L = 10^{\frac{(T_0 - T_b)}{Z}}$$

T_0 ＝ 滅菌器内又は滅菌物内の温度
T_b ＝ 滅菌基準温度（121℃）

$$F_0 = \int_{t_0}^{t_1} L\,dt$$

$t_1 - t_0$ ＝ 処理時間（分）

2．パラメトリックリリース許容滅菌条件

パラメトリックリリースの適用を考えている医薬品には、当該医薬品の熱安定性並びに滅菌前製品に対するバイオバーデン管理を考慮に入れ、以下の中から適切な滅菌条件を選択する。尚、日本薬局方の製剤総則、通則6を満たす場合には、下記以外の条件でもパラメトリックリリースを考えることができる。

方法	熱負荷量[a)]	容器当たりの最大バイオバーデン数	生菌数試験	耐熱性試験
1	121℃で 15 分間以上、又は Fo≧15	<1,000 個	定期的に実施	定期的に実施
2	Fo≧8	<100 個	定期的に実施	定期的に実施
3	Fo≧4	<100 個	ロット毎に実施	ロット毎に実施
4	Fo≧2	無菌製造法（SAL<10^{-3}）	ろ過前液について定期的に実施	ろ過前液について定期的に実施

a) 各載荷形態毎に計測した品温分布から決定した、コールドスポットにおける製品に対する熱負荷量とする。

3．　要管理項目

高圧蒸気滅菌における重要管理項目を以下に示す。

a) 熱履歴（通例，F_0値で表示）

b) 温度

c) 圧力

d) 時間

e) 製品の載荷形態

f) その他，必要な事項

4．ユーティリティ

高圧蒸気滅菌に必要なユーティリティ及び制御装置については、その品質及び精度を定めること。

a) 使用する蒸気の品質

b) 滅菌器の中に圧戻し等のため導入する空気の品質

c) 冷却のため用いる水の品質

d) 温度制御装置の精度

e) 圧力制御装置の精度

f) 時間制御装置の精度

g) その他

5．　微生物の管理プログラム

パラメトリックリリースを採用する場合、原料、容器／栓及び滅菌前製品中のバイオバーデン管理が重要である。バイオバーデン数を予め定められた方法及び頻度によって測定し、必要に応じて検出された微生物の性状検査、熱抵抗性を調べる。また、医薬品製造区域における環境微生物の評価方法については、「無菌医薬品製造区域の微生物評価試験法」を参照すること。

5.1 生菌数試験：日本薬局方「微生物限度試験法」の「生菌数試験」を準用する。

5.2 耐熱性試験：大容量製剤（100 mL 以上）の場合は1容器量、小容量製剤の場合は 10 容器相当量又は 100 mL 容量のうち多い容量を試料とし、80℃以上で 60 分間熱処理後、ソイビーン・カゼイン・ダイジェスト培地を用い、37℃又は 55℃で1週間培養する。菌の発育が認められたら当該菌の D 値を測定又は推定し、パラメトリックリリースの設定条件を満たしているかどうかを確認する。

6．バイオロジカルインジケータ（BI）

通常、パラメトリックリリースを適用する滅菌工程の日常管理には BI を使用しない。滅菌バリデーション及び滅菌工程の定期的検証に用いる BI は、その仕様を規定し、文書化すること。定期的検証に用いる BI は、その形状、製品又は模擬製品への負荷形態等は、微生物学的稼働性能適格性の確認を行う際に用いたものと同一又は同等以上の抵抗性を持つことが確認されたものでなければならない。

7．変更管理システムの確立

滅菌に係わる品質に大きな影響を及ぼす滅菌装置、載荷形態及び滅菌条件等の変更は、当該医薬品のパラメトリックリリース条件の変更に該当する。滅菌バリデーション手順書に変更管理システムを定め、予め特定した変動要因の変更に当たっては、変動要因やその許容条件が引き続き目的とする品質に適合する医薬品を恒常的に保証することが妥当であることを検証しなければならない。また、バリデートされた滅菌工程での変更を実施するに先立ち、適切な責任組織より当該変更の実施についての承認を受ける必要がある。

8．出荷手順

最終滅菌製品のパラメトリックリリースによる出荷に必要な条件を明記した出荷手順書を作成すること。出荷に当たって評価すべき記録としては、以下のものが含まれる。

a) バッチ記録

b) 製造環境の微生物評価データ

c) 原料，滅菌前製品のバイオバーデンデータ

d) 滅菌指標体に関するデータ

e) 滅菌工程及び滅菌工程を支援するシステムの維持管理に関するデータ

f) 滅菌パラメータの管理に関するデータ

g) 計器の校正に関するデータ

h) 再バリデーションデータ

i) その他

参考資料

1．載荷形態と品温

製品の載荷形態は熱容量、被滅菌物の品温と密接な関係があるので、製品の基本的な載荷形態ごとに温度上昇と品温に関してバリデーションを行い、載荷形態図を完備しておかなければならない。熱容量が変化するような載荷形態をとるときは、再バリデーションが必要である。

2．高圧蒸気滅菌におけるユーティリティの精度

ISO 11134 に定める装置の望ましい精度及び事項は以下の通りである.

2.1 温度制御装置

a）ディジタル又はアナログ装置を使用

b）50℃から 150℃の範囲で±1%の精度を有すること

c）滅菌温度で±0.5℃に調節されること

d）温度計破壊保護装置を有すること

e）装置の分解をせずに鍵，コード又は器具の使用で調整できること

2.2 圧力制御装置

a）ディジタル又はアナログ装置を使用

b）0 から 5 気圧の範囲で±1.6%，あるいはこれより精度がよいこと

c）圧力計破壊保護装置を有すること

d）装置の分解をせずに鍵，コード又は器具の使用で調整できること

2.3 時間制御装置

a）5 分以上の時間の場合は，±1%以内

b）5 分以内の時間の場合は，±2.5%以内

2.4 蒸気の品質（下記規格値は、製品と蒸気が直接接触する医療用具を対象にしたものであり、密封容器に充填された医薬品の場合は、必ずしも本規格を満たす必要はない)。

a）乾燥度：0.95 以上

b）非凝縮気体：3.5% (v/v)以下

c）過熱：5℃以下

d）蒸気圧変動：滅菌器減圧弁前の蒸気圧力変動は 10%を超えず，減圧比は 2 対 1 以上

e）滅菌蒸気及びボイラーの給水基準値

f）滅菌蒸気凝縮水：USP の WFI 規格に準拠した水を用いる

2.5 導入空気の品質

a）0.3μm 以上の粒子を 99.5%以上捕足する能力を有するフィルターを通過

b）油量は 1 m^3 当り 0.5 mg 以下

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分担研究報告書

医薬品の品質保証基準及び品質判定システムに関する研究
――ＧＭＰ調査の経験等を踏まえたパラメトリックリリースの実施に関する考察――

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研究要旨　ＧＭＰに関する調査及び文献調査をもとに、ロットごとに行う無菌試験に代えてパラメトリックリリースが適用できる条件等について検討した。最終滅菌医薬品については、適正なバリデーションの実施のもとに、滅菌工程の重要管理項目等を厳しく管理、評価することにより、パラメトリックリリースを適用することが可能になると考えられる。

Ａ．研究目的

平成11年10月の医薬品承認審査ハーモナイゼーション国際会議(ICH)において、「規格及び試験方法に関するガイドライン」（Q6A）が最終合意に到達した。これを受けて、このガイドラインにある定期的試験/スキップ試験、工程内試験、パラメトリックリリースなどの実施に向けての法的整備が必要となったため、平成11年12月に告示された第13改正日本薬局方第二追補では通則第4項の改正が行われるに至った。即ち、通則第4項に「製造工程のバリデーション又は品質管理の試験検査に関する記録により、品質が日本薬局方に適合することが保証される場合には、出荷時の検査等において、必要に応じて各条の規格の一部について試験を省略できる。」旨、明記されたことにより、医薬品の品質規格を定めた我が国の薬局方において、初めてバリデーションの概念が導入されたことは注目に値する。この概念はすでに米国薬局方（USP）や欧州薬局方（EP）に導入されており、国際調和の観点からも大きな意義をもっている。

本研究の目的は、このガイドラインが我が国において実施される段階で様々な問題や混乱が生じることのないように、あらかじめ実施にあたっての問題点とその対応策を検討しておくことにある。定期的試験/スキップ試験（平成10年度）及び工程内試験（平成11年度）に続き、平成12年度はパラメトリックリリースの適用の可能性について検討した。

Ｂ．研究方法

厚生省のバリデーション基準には、バリデーションの実施対象として、製造工程、製造を支援するシステム（製造用水供給システム、空気処理システム）及び洗浄等の作業が掲げられている。GMP調査の経験等を踏まえて、これらの実施対象に対するバリデーションが適正に行われているという前提のもとに、パラメトリックリリースを適用していく際に留意すべき条件等について検討を加えた。

Ｃ．研究結果

我が国では、滅菌医療用具については「滅菌バリデーション基準について」(平成9年7月1日付、医薬監第1号厚生省医薬安全局監視指導課長通知)やISO規格等を踏まえた「医療用具の滅菌バリデーションに関するガイドラインについて」(平成10年5月1日