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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

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厚生科学研究費補助金（医薬安全総合研究事業）
総括研究報告書

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

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研究要旨　パラメトリックリリースについて検討を行い、その実施は日局通則４項、製剤通則６項の改正により法的には可能であること、認可には滅菌工程がバリデートされていることを示す必要があり、地方庁の関与が必須で、製造承認書の整備が必要であることを示した。また、高圧蒸気滅菌医薬品のパラメトリックリリース指針案を作成すると共に、滅菌法を熱負荷量から４種に分け、パラメトリックリリースの許容条件案を作成した。更に、ＧＭＰの観点から、パラメトリックリリースの適用には、重要管理項目等の管理、再バリデーション等が大切であることを示した。一方、地方の製造所は設備面でパラメトリックリリース対応までに至っておらず、導入に向けて技術の確立等が必要であることを明らかとした。

定期的／スキップ試験の具体的実施法について検討を行い、スキップ試験には代わりの試験を立てる等、いくつかの方式が考えられることを示し、単純にスキップする方式は、医薬品の有効性、安全性に密接に関連する試験項目への適用を避けるのが望ましく、確認試験等に適用可能なことを示した。そして、スキップ試験の実施、中止、再開の規則案を作成した。更に、含量均一性試験について、質量偏差試験またはサンプル数の少ない試験を代わりの試験として使用できる条件を明らかにすると共に、市販製剤の大部分にスキップ試験を適用し得ることを示した。また、主薬濃度のばらつきが大きい製剤、カプセルに対しスキップ試験を適用できる条件を示した。

分担研究者
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A．研究目的

ICH で検討されてきた規格及び試験方法のガイドライン（Q6A）は、1999 年 10 月、最終合意に達するに至った。このガイドラインには、1)定期的試験／スキップ試験，2)工程内試験，3)パラメトリックリリースといった我が国の承認・許可制度にない考え方が導入されている。ガイドラインが最終合意に達した今、これらの考え方を我が国で実行するため、適用可能な試験項目、適用できる条件を明らかにし、法的・行政的に実施できる体制を早急に確立する必要がある。本研究は、我が国において、上記の考え方の試験を実施する上での問題点を明らかにし、実施手順の確立を目指すものである。

本年度は、パラメトリックリリースについて、実施に向けての体制、適用条件等について検討を行った。また、スキップ試験の実施に向けて、適用、実施の具体的ルール等について検討を行うと共に、個別の試験項目として、含量均一性試験へのスキップ試験の適用条件について検討を行った。

B．研究方法

１．パラメトリックリリース

高圧蒸気滅菌について現状調査、ＥＵの専門家会議への参加、米国 Baxter 社の専門家との意見交換、ISO 国内委員との意見交換を行い、高圧蒸気滅菌のパラメトリックリリース指針案を作成した。また、GMP の観点からパラメトリックリリースを適用する際の留意すべき条件等について検討を加えると共に、富山県の製造企業を対象にパラメトリックリリースに関する調査を行った。

２．定期的／スキップ試験

スキップ試験の欧米の実施状況を調査すると共に、実施の方式、規則等について検討を行った。また、含量均一性試験をスキップ試験とするための条件について、統計的に検討を行った。

C．研究結果

1．パラメトリックリリース

1）法的、行政的対応　　日局通則４項、製剤通則６項の改正により、パラメトリックリリースの受け入れは既に法的には整備された。パラメトリックリリースの認可には地方庁の関与が必須で、製造承認書の整備としては、「製造方法」欄および「規格試験法」欄に滅菌方法並びに無菌試験等に関する記載を追加する必要があろう。認可に際しては、規制当局に製品の滅菌工程が適正にバリデートされていることを示す必要があり、さらに、適用後も定期的に再バリデーションを行い、滅菌工程が恒常的にバリデートされていることを示す必要がある。

2）パラメトリックリリースの指針　　高圧蒸気滅菌医薬品について検討を行い、パラメトリックリリース許容滅菌条件、重要管理項目、ユーティリティ、微生物の管理プログラム等を定めた指針案を作成した。

3）GMP の観点からの検討　　パラメトリックリリースを適用するには、滅菌工程の適正なバリデーション、滅菌保証の再現性が不可欠で、定期的な再バリデーションの実施が重要であること、製造記録等による滅菌保証の評価方法の標準化並びに滅菌工程の安定性の評価が必要になること、バイオバーデンのモニタリング及び製造用水の微生物管理が重要であることを示した。

また、製造所について調査を行い、滅菌条件設定にバイオバーデンまで含めて検討している例は少ないこと、製品及び環境中のバイオバーデンの測定頻度は製造所によって大分異なること、現在の滅菌バリデーション、製造設備でパラメトリックリリースに対応することは難しいこと、導入の問題点として要件やパラメータの管理の難しさがあることが分かった。無菌性保証のためには、パラメトリックリリースが望ましいことを各社ともよく理解しているが、一方で、無菌試験適合医薬品の製造継続を望んでいることも判明した。

2．定期的試験・スキップ試験

1）実施の方式　　a)単純にスキップする方式、b）代わりの試験を立ててスキップする方式、c）サンプル数を減らした試験を適用してスキップする方式が考えられる。単純にスキップする方式は、有効性又は安全性と密接に関係する試験項目への適用は避けるべきであり、特異性の高い定量法が用いられている医薬品の確認試験、残留溶媒への適用が可能と思われる。

2）適用の一般原則　　スキップ試験を適用するには、1）主要な変動要因の解析、特定、2）変動要因の制御、3）最終製品の品質の確認が必須である。スキップ試験が適用されるのは、原則として製造が多い製品で、スキップ試験開始後は、管理図で許容域を超えていないことを確認する必要がある。また、試験結果がスキップ試験の判定基準に適合しなかった場合、スキップ試験を中止し、規格値に適合していないロットが見出された場合、直ちに当該ロットを回収する必要がある。スキップ試験を再開するには、中止の原因の究明が必須である。

3）含量均一性試験への適用　　主薬濃度（主薬量／１個の製剤質量）RSD が 2%以下であれば、質量偏差試験を代わりの試験として使用できることが OC 曲線より明らか

となった。市販製剤の多くは、主薬濃度 RSD が 2%以下でスキップ試験を適用できる可能性は高い。また、主薬濃度のばらつきが大きくても、判定値を厳しくすることにより質量偏差試験の適用が可能で、判定係数を変えればサンプル数を減らした含量均一性試験を代わりの試験として使用できることが分かった。更に、硬カプセル剤においても、カプセル総質量を用いた質量偏差試験を代わりの試験として使用できることが判明した。

D.考察

1．パラメトリックリリース　　日本薬局方ではこれまで無菌医薬品の製法にかかわらず無菌試験が実施が義務付けられていたこともあり、わが国の多くの製薬企業ではまだパラメトリックリリースについて検討されていない。しかし、無菌試験の感度（SAL=10^{-2}）から考えても高圧蒸気滅菌医薬品（SAL<10^{-6}）に、パラメトリックリリースを適用することが望ましく、滅菌工程のバリデーションが適正に行われているならば、パラメトリックリリースを推進すべきである。パラメトリックリリース指針案作成段階における大きな議論は、パラメトリックリリースの許容条件と耐熱性菌に対する評価試験法であった。パラメトリックリリースの許容条件に関しては、4 種の方法を提示したが、特に、無菌操作法で製した無菌医薬品を Fo≧2 の熱処理した場合もパラメトリックリリース許容条件の一つに加えたことは、今後、国際的にも議論の対象になると考えられる。

パラメトリックリリースでは最終製品の試験結果によるのではなく、滅菌工程の管理パラメータ及び製造記録等に基づいて出荷の可否を判断することになる。したがって、製造記録等による滅菌保証の評価方法の標準化並びに滅菌工程の安定性を評価するため、管理パラメータのトレンド解析など内部監査体制を構築しておくことも必要であると考えられる。

今後の課題は、1）パラメトリックリリース指針の早期発行、2）許可要件に関する地方庁向けの Q&A 作成、3）121℃で 15 分以上又は Fo≧8 処理医薬品に対するパラメトリックリリースの導入勧告、4）パラメトリックリリース導入企業に対する GMP 査察の強化である。

2．定期的試験・スキップ試験

欧米におけるスキップ試験の実施状況を調査した結果、EU 行政当局は、要求は厳しいがスキップ試験を認めており、FDA はなかなか認めていないことが分かった。これら欧米の実施状況を考えるとき、スキップ試験は決して安易に認められる性格のものではない。しかし、間違いなく合格するような試験項目に関しては認めていくべきであろう。但し、適用に際しては、1）実生産スケールで主要な変動要因を明らかにし、2）製造工程を GMP で適切に管理されていることが重要で、それらの前提条件が満たされて適用が可能となることに留意する必要がある。

スキップ試験の実施方式にはいくつかあるが、代わりの試験を立ててスキップする方式で用いられる「代わりの試験」は、規格に設定された試験と同等以上の精度を有する「代替法」（日局通則 32 項）と区別する必要がある。単純にスキップする方式は、スキップしたロットに関しては何のデータもない状態となるため、医薬品の有効性、安全性上、重要な試験に適用するのは適切でない。これらに対しては、代わりに立てた試験をロット毎に行うことにより、当該項目の試験をスキップする方式を採用することが勧められる．

E．結論

1．パラメトリックリリース

パラメトリックリリースの実施は、日局通則 4 項、製剤通則 6 項の改正により法的には可能である。認可には滅菌工程がバリデートされていることを示す必要があり、地方庁の関与が必須で、製造承認書の整備が必要であると思われる。また、許容滅菌条件、重要管理項目、ユーティリティ、微生物の管理プログラム等を定めた高圧蒸気滅菌医薬品のパラメトリックリリース指

針案を作成したので、我が国においては指針案に従った適用が望まれる。GMPの観点からは、パラメトリックリリースの適用には、重要管理項目等の管理、再バリデーション等が大切であるが、製造所の設備面がパラメトリックリリースに対応しておらず、導入に向けて技術の確立等が必要と思われる。

2．定期的／スキップ試験

スキップ試験には代わりの試験を立てる等、いくつかの実施方式が考えられる。しかし、単純にスキップする方式は、医薬品の有効性、安全性に密接に関連する試験項目への適用を避けるべきで、確認試験等に適用可能と思われる。また、スキップ試験の実施、中止、再開の規則案を作成したので、これに準じて運用されることが望まれる。

含量均一性試験へのスキップ試験の適用に関しては、主薬濃度 RSD が 2%以下であれば質量偏差試験を代わりの試験として使用できることが判明した。市販製剤の大部分は主薬濃度 RSD が 2%以下で、スキップ試験を適用し得るものと思われる。また、代わりの試験としてサンプル数を減らした試験を適用できること、主薬濃度のばらつきが大きい製剤、カプセルに対しスキップ試験を適用できる条件を示した。

F．研究発表

1) 鈴木英世、横田洋一、津野敏紀、富山県における工程内試験成績の出荷試験への利用調査と考察、富山県薬事研究所年報、27，114-116 (2000).
2) 佐々木次雄、中村晃忠、医薬品製造における高圧蒸気滅菌の現状調査、医薬品研究 31，883-983 (2000).

G．知的所有権の取得情報

なし

厚生科学研究費補助金（医薬安全総合研究事業）
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

分担研究者：佐々木次雄　国立感染症研究所　安全性研究部無菌性制御室長

研究要旨：ICH/Q6A ガイドラインに示すパラメトリックリリースとは、主に最終滅菌医薬品に適用されるものである。しかし、日本薬局方の製剤通則「注射剤」には製法にかかわらず無菌試験の実施が義務付けられており、これまではパラメトリックリリースは適用できなかった。そこで、平成 13 年 3 月に公布される第 14 改正日本薬局方の製剤総則・通則 6 項にパラメトリックリリースが明記されることになり、法的にもパラメトリックリリースが許容されることになった。そこで、国際的にも許容され、わが国に導入可能な高圧蒸気滅菌医薬品に対するパラメトリックリリースを検討し、その指針案を作成した。

A. 研究目的

ICH/Q6A ガイドラインに記載されているパラメトリックリリースを国内製薬企業に導入させるための第一歩として、高圧蒸気滅菌医薬品に対するパラメトリックリリースを検討し、その結果を行政に反映させる。

B. 研究方法

分担研究者は、本研究事業の最終年度のみ参加し、以下の方法で研究を実施した。1）国内製薬企業における医薬品製造における高圧蒸気滅菌の現状調査、2）ＥＵのパラメトリックリリース指針に対する専門家会議に参加、3）1985 年より最終滅菌医薬品にパラメトリックリリースを適用している米国 Baxter 社の専門家との意見交換、4）医療製品（health care products）に対する高圧蒸気滅菌法の国際規格を作成している ISO/TC198/WG3 国内委員との意見交換を経て、パラメトリックリリース指針案を作成。

（倫理面への配慮）　特になし

C. 研究結果

国内製薬企業における医薬品製造における高圧蒸気滅菌の現状調査を研究発表 1 に、ＥＵガイドラインに対するコメントを研究発表 2 に、Baxter 社の専門家との意見交換を研究発表 3 に、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を研究発表 4 に示す。

D. 考　察

無菌試験の感度（SAL=10^{-2}）から考えても高圧蒸気滅菌医薬品（SAL<10^{-6}）には、無菌試験での出荷より重要パラメーターや滅菌に要するユーテイリテイを十分管理して出荷させた方がより高品質の無菌医薬品を供給できることは明らかである。日本薬局方ではこれまで無菌医薬品の製法にかかわらず無菌試験が実施が義務付けられていたこともあり、わが国の多くの製薬企業ではまだパラメトリックリリースについて検討されていない。企業からは、パラメトリックリリースが導入されても出荷期間が短縮されるだけであり、逆に滅菌要件が厳しくなりメリットはないとの意見も多く聞かれた。しかし、中には積極的にパラメトリックリリースの導入を検討している企業もあり、その努力を行政的にも評価する必要が

ある。パラメトリックリリース指針案作成段階において、最も大きな議論は、パラメトリックリリースの許容条件と耐熱性菌に対する評価試験法であった。パラメトリックリリースの許容条件に関しては、表１に示す方法を提示した。特に、無菌操作法で製した無菌医薬品を Fo≧2 の熱処理した場合もパラメトリックリリース許容条件の一つに加えたことは、今後、国際的にも議論の対象になると考えられる。耐熱性菌に対する評価試験法も種々議論があったが、結局、規定量の滅菌前製品を 80℃以上で 60 分間処理後、SCD 培地にて 37℃又は 55℃で１週間培養することを提案した。

E. 結　論

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を作成できたので、今後の課題としては、１）行政府からのパラメトリックリリース指針の早期発行、２）必要に応じてパラメトリックリリース許可要件に関する地方庁向けの Q&A 作成、３）121℃で 15 分以上又は Fo≧8 処理医薬品に対するパラメトリックリリースの導入勧告、４）パラメトリックリリース導入企業（とりわけ低 Fo 値採用企業）に対する GMP 査察の強化が望まれる。

F. 研究発表(本研究事業に関連するもののみ)

１．　佐々木次雄、中村晃忠。医薬品製造における高圧蒸気滅菌の現状調査、医薬品研究 31(12): 883-983, 2000.

２．　EU GMP Guide/Draft Annex に対する PDA Task Force Comment (September 29, 2000)

３．Baxter 社のパラメトリックリリースに関する基本的考え

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

５．佐々木次雄、中村晃忠、三瀬勝利。日本薬局方に準拠した滅菌法及び微生物殺滅法、日本規格協会、1998.

６．佐々木次雄、川村邦夫、水田泰一。ISO 規格に準拠した無菌医薬品の製造管理と品質保証、日本規格協会、2000.

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

20000806

資料1および資料3は雑誌/図書に掲載された論文となりますので、

下記の資料をご参照ください。

医薬品製造における高圧蒸気滅菌の現状調査.

佐々木次雄、中村晃忠

医薬品研究. 2000 31(12) :883-893.

資料 2

PDA
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Tel: (301) 986-0293
Fax: (301) 986-0296
www.pda.org

September 29, 2000

Dr. Ph. Brunet, Head of Unit
European Commission
Enterprise Directorate, Pharmaceuticals and Cosmetics
Rue de la Loi 200
B-1049 Brussels
Belgium

Ref: EU GMP Guide, Annex 17, Parametric Release, Draft, 6 April 2000.

Dear Dr. Brunet:

Enclosed please find PDA comments on draft Annex 17 referenced above. PDA is an international professional association of more than 9,000 individual member scientists having an interest in the fields of pharmaceutical manufacturing and quality. A substantial number of our members work for pharmaceutical companies located in the European Union, and many others work for international companies that will be affected by the implementation of Annex 17. Our comments have been prepared by a group of international experts in the fields of validation and regulatory affairs.

Immediately following are our major comments. Attached also find an annotated draft of Annex 17 showing revised, deleted and added text, and an explanation for each. We trust our comments will be useful in preparation of the final guidance.

Major Comments

1. The Annex is written as guidance for inspectors rather than for manufacturers. The draft annex is an almost verbatim copy of PIC/S guidance (PR 2/99-1, October 1999) for parametric release which contains inspection guidance for the GMP inspectorates and information on collaboration between inspectors and marketing authority assessors. Such guidance is inappropriate for inclusion in the EU GMP Guide, the purpose of which (according to the Introduction) is to provide "sufficient detail for manufacturers to be made aware of the essential matters to be considered when implementing the [GMP] principle."

2. The safety (sterility) of sterile medicinal products is contingent on process validation, monitoring and control of the manufacturing operations, not in the sterility test. GMP requirements for sterile product release should be applied to all manufacturers of such products irrespective of whether a company chooses to perform a sterility test or apply for release based on control of parameters. Regulatory approval of parametric release, on the other hand, is an administrative decision involving the amount and type of data the approving authority will require in order to make a decision about approval. The Annex seems to confuse the difference, suggesting at times that implementation of parametric release may require more rigorous GMP controls on the part of the manufacturer.

3. New GMP guidance for sterile medicinal products should be in a revised Annex 1. Draft Annex 17 contains much guidance which more properly belongs in Annex 1 of the EU GMP Guide, "Manufacture of Sterile Medicinal Products." Some of this guidance goes to a greater level of detail than the current Annex 1 and, in some cases, proposes more stringent controls than the current EU requirements. Public discussion of such guidance could occur during the revision of Annex 1.

4. Parametric release for other types of testing should be in a different guidance. The approval of parametric release for testing other than the sterility test (e.g., testing of starting material, in process and final product testing) involves issues that are very different from terminal sterilization. In order to maintain the utility of the current document, other uses of parametric release should be deleted from this draft and addressed in a separate technical guidance.

5. Guidance on the use of parametric release should be incorporated in the related Note for Guidance rather than the GMP Guide. In view of points 1-4, above, PDA proposes that any revision of this guidance be converted to an annex to CPMP/QWP/3015/99, Note for Guidance on Parametric Release, where the elements that require emphasis to support parametric release can be incorporated. The Note for Guidance is the correct place where the collaboration of assessors and inspectorates can be addressed, and where the prerequisites for acceptance of parametric release are described in a general way.

Attached also please find copies of PDA Technical Report No. 30, "Parametric Release of Pharmaceuticals Terminally Sterilized by Moist Heat," which represents PDA's current thinking on this topic.

To further assist with the development of this annex PDA offers to host a public forum or workshop, on terms suitable to the authorities, to develop public dialog and expert opinion on the necessary aspects of parametric release. If you have any questions regarding our comments, or how we may assist with further development of the draft, please contact me.

Sincerely,

Edmund M. Fry
President
fry@pda.org

Enclosures: PDA annotated revision of Annex 17
PDA Technical Report No. 30, "Parametric Release of Pharmaceuticals Terminally Sterilized by Moist Heat"

1
EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL
Single market, regulatory environment, industries under vertical legislation
Pharmaceuticals and cosmetics
Brussels,7 th April 2000
ENTR/6270/00
Working Party on Control of Medicines and Inspections

Proposal for a **Annex 17** to the EU Guide to
Good Manufacturing Practice

Title: Parametric Release
First discussions within PIC/S framework June 1998- August 1999
Consultation with Ad-hoc meeting of GMP Inspection services September 1999 – February 2000
Revised version March 2000
Release for industry consultation 6 th April 2000
Proposed Deadline for comments September 2000

Note: This document has been released for parallel industry consultation according to the PIC/S scheme ref: PR 2/99-1 of October 1999, Annex 9 to the PIC/S guide.
It should be read in conjunction with CPMP/QWP/3015/99 Note for Guidance on Parametric Release which was released for consultation by the EMEA in March 2000 also with a deadline for comments of September 2000.

Table of Contents

1. General Introduction

1.1 The term Parametric Release is used in several different ways in the Pharmaceutical Industry. The definition of Parametric Release used in this document is based on that proposed by the European Organization for Quality: " A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process. ~~and on the compliance with specific GMP requirements related to Parametric Release."~~

[Explanation: There is no specific GMP related to parametric release. See covering letter.]

2. Purpose

2.1 The purpose of the document is to provide guidance for *industry and competent authorities concerning the expected procedures and measures in cases where* ~~the GMP Inspectorate to use during preparation for inspections of company premises where~~ Parametric Release *to replace the sterility test* has been approved or applied for. ~~In addition the document provides a framework for GMP inspectors and Marketing Authorisation assessors to work together and jointly approve an application for Parametric Release.~~

[Explantion: See General Comments in covering letter.]

3. Scope

3.1 This guidance ~~attempts to~~ covers *only the elimination of the sterility test based on approval of parametric release for terminally sterilized medicinal product.* ~~a wide scope that includes a reduction or elimination of routine testing in the fields of starting materials, in process and finished product testing. Within the Finished Product testing group the elimination of routine sterility testing is a primary focus of interest. The document is organised to accommodate this focus of interest.~~

[Explanation: Scope should be limited to parametric release. See covering letter.]

4. Definitions / Glossary

~~**Failure Mode Effect Analysis--FMEA**~~
~~An analysis of the process that assigns a numerical value on a defined scale (1 to 5 or 1 to 10 are most commonly used) to the following:~~

~~- probability of failure of a defined stage,~~
~~- probability that the failure will be detected before the product is released,~~
~~- severity of consequence if the product is released.~~

~~The numerical values are multiplied to produce a score. The magnitude of the score determines the priority with which the failure mode has to be prevented or controlled. More information can be found in R.G. Keiffer and A. Borgmann 'Applications of Failure Mode Effect Analysis in the Pharmaceutical Industry' Pharmaceutical Technology Europe, September 1997.~~

~~**Hazard Analysis and Critical Control Points--HACCP**~~
~~A systematic documented analysis of the process that identifies pivotal points of control and provides the details of methods of control with defined tolerances.~~
~~More information can be obtained from HACCP a Practical Guide, Technical Manual No. 38 from the Food Research Association Chipping Campden, Gloucestershire GL55 6LD England Tel 01386 8402319.~~

[Explanation: Delete. FMEA and HACCP are concepts which are not generally used in the manufacture of pharmaceuticals today. (These concepts are widely recognized in the Device Industry.) To establish FMEA and HACCP as official methods for analyzing pharmaceutical manufacturing processes, would require the creation of a respective guideline and a broad discussion and consensus in the pharmaceutical field. It is inappropriate to introduce these quality concepts in the context of parametric release, where end product testing of limited diagnostic value

is to be replaced by GMP-compliant procedures. It should be up to the individual company to choose and justify analysis mechanisms for their processes.]

Parametric Release
A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing ~~process and on the compliance with specific GMP requirements related to Parametric Release~~.

[Explanation: There is no specific GMP requirement for parametric release.]

~~**Reduction of human error**~~
~~An analysis of the process from the point of view of the people operating it that takes into account known human fallibility's and provides ways to minimise their effects. The analysis should also include automated processes, software creation and use etc.~~

[Explanation: Delete this term as the reduction of human error, human or otherwise, is the fundamental concept behind GMP, risk analysis procedures, validation of automated processes, validation of software, etc.]

Sterility Assurance System
The sum total of the arrangements made to assure the sterility of products. For terminally sterilized products these typically include the following stages:

(a) Product design.
(b) Knowledge of and, if possible, control of the microbiological condition of starting materials and process aids (e.g. gases and lubricants).
(c) Control of the contamination of the process of manufacture to avoid
The *potential for* ingress of microorganisms and *for them to subsequently multiply* ~~their multiplication~~ in the product.
~~This is usually accomplished by cleaning and sanitization of product contact surfaces, prevention of aerial contamination by handling in clean rooms, use of process control time limits and, if applicable, filtration stages.~~

[Explanation: Delete as this level of guidance is too detailed for this general part of the document which should be intended to give advice for parametric release and not to rewrite basic GMP requirements.]

~~(d)~~ Prevention of mix up between sterile and non sterile product streams.
~~(e) Maintenance of product integrity.~~

[Explanation: Delete item (e) as parametric release is intended to replace sterility testing, and not to guarantee integrity over shelf life, which is not assured by a sterility test. If needed, there should be a special section related to container closure integrity, perhaps under product design.]

(f) The sterilization process.
~~(g) The totality of the Quality System that contains the Sterility Assurance System e.g. change control, training, written procedures, release checks, planned preventative maintenance, failure mode analysis, prevention of human error, validation calibration, etc.~~

[Explanation: Clarity. The total quality system is not a stage of the sterility assurance system.]

5. PART I

ELIMINATION OF ROUTINE STERILITY TESTING FOR PARAMETRIC RELEASE

5.1 Introduction

5.1.1 This section is only concerned with that part of Parametric Release which deals with the routine release of finished products without carrying out a sterility test. ~~Elimination of the sterility test.~~*Any* sterilization *process, whether pharmacopoeial standard conditions are applied*

or not, is only valid on the basis of successful demonstration that predetermined, validated sterilising conditions have been achieved.

> ***[Explanation: A non-validated sterilization procedure cannot be made valid by a sterility test with its known statistical insignificance. This is true for standard and non-standard sterilization processes.]***

5.1.2 It is generally recognised that a sterility test only provides an opportunity to detect a major failure of the sterility assurance system which should be more reliably detected by other means. ~~On the other hand the sterility test does provide the last chance to detect a failure and must be retained to challen ge inherently insecure operations like aseptic processing.~~

> ***[Explanation: Delete. While it is true that sterility testing may provide an opportunity to detect a sterility failure, a negative result does not by any means provide an assurance that the product is sterile. The statistical limitations of the sterility test dictate that its value should not be over-emphasized. Futher, the draft deals exclusively with products terminally sterilized in their final containers. While it can be argued if aseptic processing operations are inherently insecure, such processes are not in the scope of the draft.]***

5.1.3 ~~Elimination of the routine sterility test may become acceptable as advances in technology are applied and the commitment to maintain rigorous quality systems matures. This aspect of~~ Parametric Release can take place if the data demonstrating correct processing of the batch provides sufficient assurance, on its own, that the process designed and validated to ensure the sterility of the product has been delivered and providing the following Principles have been respected.

> ***[Explanation: The wording of the section is vague and the intent is inconsistent with the purpose of the document which sould be to define what industry needs to do from the GMP perspective to support parametric release. Delete first three words of second sentence for clarification.]***

5.2 Principles

5.2.1 Elimination of routine sterility testing can *at present* only be approved for products terminally sterilized in their final container.

> ***[Explanation: Clarification]***

5.2.2 Sterilization methods ~~according to Euro. Ph. requirements~~ using steam, dry heat and ionising radiation *which are accepted as being fully GMP compliant based on the guidance given by the pharmacopoeias and guidance documents of the regulating authorities* may be considered.

> ***[Explanation: With respect to the present focus on mutual international recognition, this document should not focus exclusively on the European Pharmacopoeia, but remain open to procedures accepted by other regulating authorities in the process of MRA. In any case, there are other official documents even from the EU, which should be considered here (e.g. EMEA decision trees).]***

5.2.3 In the event of *unacceptable* deviations in the sterility assurance system a satisfactory result from a sterility test provides no evidence to justify the release of a batch of product. ~~This applies under any circumstance even if elimination of routine sterility testing has been authorised.~~

> ***[Explanation: Not every possible deviation in the sterility assurance system must be considered critical. Critical parameters need to be defined. Delete last sentence. The draft should be specifically intended for parametric relese and not be a general GMP rewrite.]***

5.2.4 Authorisation for elimination of routine sterility testing should be given, refused or withdrawn jointly by those responsible for assessing products together with the GMP inspectors. *The details of this collaboration are described in CPMP/QWP/3015/99 draft.*

> ***[Explanation: Clarification.]***

~~5.2.5 This document only addresses the aspects that the GMP inspectors will consider. The features that are clearly the province of the assessors include the following aspects of product and process design and their initial validation. These factors would also be checked by GMP inspectors on site:~~

~~(a) The assurance of product integrity under all relevant conditions.~~
~~(b) The capability of the sterilization agent to penetrate to all relevant parts of the product.~~
~~(c) The choice of a suitable sterilization process.~~
~~(d) The compliance with microbiological limits.~~

[Explanation: Delete. This document should not be addressed to inspectors. Details of the requirements are given under 7 and do not need to be restated here.]

~~5.2.6 It is unlikely that a completely new product would be considered as suitable for Parametric Release because a period of satisfactory sterility test results will form part of the acceptance criteria. There may be cases when a new product is only a minor variation, from the sterility assurance point of view, and existing sterility test data from other products could be considered as relevant.~~

[Explanation: Delete. This is assessor information. Further, as parametric release is based on process control, acceptance should be connected with a process and its associated quality assurance and not with historic sterility testing results for an individual product.]

~~5.2.7 It is unlikely that approvals en bloc for a site would be considered.~~

[Explanation: Delete. This is assessor information. Further, as parametric release is based on process control, acceptance should be connected with a process and its associated quality assurance and not with historic sterility testing results for an individual product. Approval en bloc for products manufactured according to the same approved procedures may be possible.]

5.3 The general basis for authorisation by the GMP Inspectorate

~~5.3.1 The secure application of elimination of routine sterility testing as part of a company's quality system will depend on the commitment of the company officers to maintain compliance to GMP at a high level across the whole scope of the operations. This should be a matter of general policy and not just reserved for the sterility assurance system. The evaluation of the historical compliance to GMP as well as current compliance would form one of the first steps carried out by the inspector. An evaluation as good to excellent is expected for successful applicants.~~

[Explanation: Delete. This describes the information an Inspectorate may consider in making their decision. In addition, we are not aware of any unified system where a company's GMP is ranked from good to excellent (or otherwise). The milestone for an approval is generally the actual GMP compliance and not what is called "historical compliance to GMP."
This type of guidance suggests a basic distrust in parametric release and an overtrust in sterility test. This could be interpreted that a company which is not committed to GMP would still be acceptable to produce sterile product as long as the sterility test is being performed.]

5.3.2 The history ~~of non sterility of product and of results~~ of *the* sterility tests *results* carried out on the product in question ~~together~~ *and/or of* ~~with~~ products processed through the same or a similar sterility assurance system should be taken into consideration.

[Explanation: Clarification. The history should be directed to the sterility assurance of the process and not to a specific product. "Similar" should be more clearly defined or guidance given so that there is consistent judgement of "similar."]

5.3.3 The sterility assurance system should be evaluated by inspection and review of documents and found to be *in compliance with GMP.* ~~fully capable and robust.~~ Appendix 1 expands upon this.

[Explanation: There must be a clear standard against which the inspection should be conducted. "Capable and robust" is not a defined description of a quality standard.]

5.4 The mechanism of authorisation

5.4.1 An application to vary a marketing authorisation or a group of similar authorisations should be evaluated in an order agreed between assessors and inspectors.

5.4.2 The inspector involved in evaluation and inspection should have specific training in inspecting and evaluating sterility assurance systems. It may be of value to include an appropriately qualified assessor on the inspection.

5.4.3 Providing the inspector's evaluation is satisfactory the Inspectorate is in a position to recommend that sterility testing may be eliminated for a group of products or like products.

5.4.4 Given Inspectorate approval and depending on the results of the evaluation of the assessors a licence varied to authorise elimination of routine sterility testing may be issued.

5.4.5 If the assessor's or Inspectorates' confidence in the elimination of sterility testing for a company's products is reduced, either group should have a mechanism to withdraw approval. Confidence may be reduced following a subsequent inspection, or on receipt of other information.

[Explanation: Delete the entire section as it describes authorisation and assessor information. The general procedures for collaboration between inspectorates and assessors is addressed in the CPMP draft. In that guidance, it should be made clear that a positive inspection of the GMP inspectors should lead to the evaluation to accept the elimination of routine sterility testing.]

6. PART II

REDUCTION OR ELIMINATION OF OTHER FINISHED PRODUCT TESTING AND STARTING MATERIALS AND IN-PROCESS TESTING FOR PARAMETRIC RELEASE

6.1 Introduction

6.1.1 This section is concerned with Parametric Release apart from the elimination of routine sterility testing which is covered in Part I.

6.1.2 It is recognised that the assurance with which starting materials can be accepted depends on many aspects of the manufacturing and the supply chain and that sampling and testing may be reduced without compromising the finished product.

6.1.3 Similarly in-process testing may be reduced on the basis of history and the introduction of different types of testing at other stages in the process. A comprehensive set of in-process tests and controls may provide greater assurance of the finished product meeting specification than finished product testing.

6.2 Principles

6.2.1 Authorisation for the reduction or elimination of starting material, in-process, or finished product testing should be given refused or withdrawn jointly by those responsible for assessing products together with the GMP inspectors.

6.2.2 This document only addresses the aspects that the GMP inspectors will consider. Matters that were defined in the product licence prior to the application for Parametric Release will require specific review by the assessors.

6.3 The general basis for authorisation by the GMP Inspectorate

6.3.1 The secure application of reduced frequency or elimination of specific tests will depend on the commitment of the company officers to maintain compliance to GMP at a high level across the whole scope of the operations.

6.3.2 The evaluation of the historical compliance to GMP as well as current compliance would form one of the first steps carried out by the inspector.

~~6.4 The mechanism of authorisation~~

~~6.4.1 An application to vary a product licence or a group of similar licences should be evaluated in an order agreed between assessors and inspectors.~~

~~6.4.2 Providing the inspector's evaluation is satisfactory the Inspectorate is in a position to recommend that the application for a product or group of like products be accepted. Approval may be qualified by requiring a running in period of reduced testing and even after full Parametric Release is operational occasional testing may be required.~~

~~6.4.3 Given Inspectorate approval and depending on the results of the evaluation of the assessors a licence varied to authorise reduction or elimination of testing for Parametric Release may be issued.~~

~~6.4.4 If following a subsequent inspection or on receipt of other information either the assessors or Inspectorates' confidence in reduction or elimination of testing for a company's products is reduced then either group should have a mechanism to withdraw approval.~~

[Explanation: Delete. Extension of parametric release to other cases than sterility testing, should not be part of this technical guideline. See covering letter.]

7. APPENDIX I

DETAILED GUIDANCE CONCERNING THE ELIMINATION OF ROUTINE STERILITY TESTING

[GENERAL REMARK
APPENDIX I needs to be substantially rewritten. It should contain only technical requirements strictly related to parametric release. As written, the present draft suggests that basic validation principles for sterilization processes become more critical once the test for sterility has been abolished. PDA strongly believes that all sterilization processes have to be properly validated. A sterility test cannot add any significant sterility assurance to a properly validated process, so there is no reason why abolishment of the sterility test should be linked to a rise of the validation requirements. Instead, emphasis should be on assurance that the process is properly validated.

Where additional GMP relevant information should be required, this should be included in an appropriate revision of GMP-Annex I, Manufacture of Sterile Medicinal Products. It should remain clear, however, that parametric release can only be a release procedure and no specific form or expansion of GMP can be created just for this case. GMP applies to all processes irrespective of the way to release a product. For this reason it is also not acceptable to formulate a general expansion to GMP-rules in a specific guideline related to parametric release.]

7.1 Introduction

~~7.1.1 This appendix provides the basis for the inspection of a sterility assurance system on site and a checklist of documents that should be reviewed. The appendix should be viewed as an expansion in detail of some aspects, rather than addition to published GMP. Therefore manufacturers of sterile products should comply with the principles expressed, whether or not they are successful in their application for Parametric Release.~~

[Explanation: Delete the entire paragraph. See General Remark. No introduction is needed at this point.]

~~7.1.2 Some of the items stray into the field of investigation originally covered by the assessor of the product licence. This is necessary to confirm continued compliance and reassessment in the full context of manufacture and the possibility of change within the constraints of the licence. It is also possible that applications for Parametric Release may relate to products covered by old licences where the level of detail documented does not meet current needs and a data gathering inspection is the best way of moving the application forward.~~

[Explanation: Delete. This section is vague, confusing and unnecessary. A clear statement would be needed that parametric release may, in part, be based on the existing documentation. Most of the paragraph seems to be an instruction to inspectors which should not be part of this document.]

~~7.1.3 The objective of the review of the sterility assurance system is to determine whether it is fully capable and robust. That is, can it achieve the objective of assuring the sterility of the product without the additional challenge of the sterility test and in addition withstand variations that may reasonably be expected.~~

[Explanation: Delete. There is no generally accepted definiton of "fully capable and robust." Further, it should not be stated that the sterility test is an additional challenge to the quality assurance system which is clearly not the case. A qualification and validation system based on a well documented risk analysis should be the basis of the Sterility Assurance System see proposal for 7.2.2]

7.2 Overall considerations

7.2.1 A clear description of the sterility assurance system should be documented and available for review. Ideally this document should reference or incorporate a detailed breakdown of each element with a formal analysis of hazards, potential failure modes of equipment and procedures and the potential for human error. Having identified these risks the document should describe how features of design, procedures and training have minimised them to acceptable levels. In addition there should be assurance that all critical failure modes that do occur will be routinely detected.

~~7.2.2 The disciplines of Hazard Analysis and Critical Control Points (HACCP) Failure Mode Effects Analysis (FMEA) and the Reduction of Human Error can provide the formal basis for such analyses.~~

7.2.2 ***A qualification and validation system based on a well documented risk analysis should be the basis of the Sterility Assurance System.***

[Explanation: Replace with new paragraph. FMEA and HACCP deleted. See comments under Definitions/Glossary.]

7.3 Personnel

7.3.1 ~~A qualified experienced sterility assurance engineer with knowledge of automated systems if applicable and a qualified microbiologist with suitable experience should normally be present~~ *Qualified supervising personnel with sufficient knowledge and suitable experience with the process should be available* on the site of production and sterilization. These people should have sufficient seniority and authority to require compliance in matters related to sterility assurance. *Duties can be delegated to equally qualified and competent individuals with sufficient authority.* ~~There may be circumstances when the presence of just one of the two sterility assurance experts is sufficient providing the other is readily available.~~

[Explanation: Modify text as shown. The legal duties of the "qualified person"(where defined) must be respected. Expertise of operators in sterile manufacture, sterility assurance and automated systems is not coupled with formal education. Rather, this depends on appropriate training and experience of staff. Eliminate terms like "sterility assurance engineer" for which there are not defined qualifications.]

7.3.2 All personnel involved in activities connected with sterility assurance should have a clear understanding of their part in the system with documented training, training reviews and retraining.

7.3.3 The number of people involved should be sufficient to cover reasonable absences due to holiday or sickness without routine overtime being worked.

[Explanation: While it may be appropriate to have this statement in this document as it is already a requirement of EU-GMP Annex 2, "reasonable" and "routine" are subjective terms and therefore open to interpretation.]

7.4 Control of product

7.4.1 The design and original validation of the product should ensure that integrity can be maintained under all relevant conditions.

7.4.2 Review of routine in-process and finished product integrity testing methods and results should demonstrate that product into which micro-organisms could penetrate will not be released for sale. ~~One of the advantages that may be lost by not carrying out the sterility test is the often functional manipulation of the product during the test which may, in the past, have revealed faults of integrity or other faults not detected by other tests. If there is evidence of product faults being detected in this way then additional testing to compensate for this should be operational before approving Parametric Release.~~

[Explanation: Delete last two sentences. 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.

Handling during the sterility test is absolutely not suited to detect general product faults. Use of automated or barrier systems is widespread during sterility testing, reducing direct handling of vials. Instead, a 100% inspection in the product packing area for leakers is a standard part of the process.]

7.4.3 The change control system should require review of change by sterility assurance personnel in addition to product engineers and licence compliance staff. ~~For example minor changes in plastic film thickness within tolerances allowed by the licence may have significant implications on micro biological integrity as well as performance during sterilization cycles.~~

[Explanation: Delete the last sentence. This is a very specific example. Suggesting that a material variance within specification tolerances can have a significant impact would question the development of the specification. If examples are to be used they should be generic.]

7.5 Control of presterilization bioburden

~~7.5.1 All relevant parts of Annex 1 "Manufacture of Sterile Medicinal Products" of the GMP Guide should be reviewed for compliance.~~

[Explanation: Delete. This section is redundant and adds no value to comply with parametric release.]

7.5.2 Although environmental control and its associated monitoring does play a part in product bioburden control it is often a relatively small part and the primary focus of attention should be on the details of determining and controlling presterilization bioburden.

7.5.3 The sampling of filled units for presterilization bioburden determination should be ~~worst case, or~~ representative of the batch, and the following should be considered:

(a) their storage conditions before testing,
(b) the time of testing in relation to the start of sterilization,
~~(c) the suitability of the method of testing, which should include tests for microorganisms resistant to the sterilizing agent, should be reviewed.~~

[Explanation: Delete as this is part of 7.5.4.]

7.5.4 The validation of the tests, the interpretation of results ~~and the way in which batch release depends on satisfactory results should also be reviewed.~~

[Explanation: Delete the second part of the sentence as this document should not be a guidance to inspectors.]

~~7.5.5 With regard to the methods used to assess bioburden there should be evidence that the company has evaluated any advantages that new technology may offer particularly in the detection of types of organism that may be resistant to the sterilization process.~~