現行治験薬GMPに対する企業の実務的な課題

（企業研究協力者からの提供情報）

◆ 現行の治験薬GMPの運用において現実に企業が直面している課題として

✓日欧米それぞれの治験に対応させた治験薬GMP対応への無駄な労力の回避
⇒現在はダブルスタンダード、トリプルスタンダードによる運用

✓日本固有の治験薬GMPの特異性の回避
・治験薬GMP三役と出荷承認システム
・治験薬製品標準書
・治験薬製造管理基準書などの特定名称の基準書

✓輸入対照薬およびそのプラセボの調達の困難性と曖昧な規定の明確化
⇒日本国内企業間では紳士協定に基づく暗黙の了解による対応

✓不明瞭なバリデーションの要件に対する明確化
⇒ベリフィケーションの概念がない

✓開発段階による差や医薬品GMPとの差に対する明確化
⇒現在は形式的な組織運営またはオーバーコントロールの両極端として実行

ICH／Q7Aの第19章のような医薬品のGMPの準用規定として、開発初期～中期にかけてはガイドライン対応とするのも一考

5

臨床治験段階の品質保証について

2007年2月28日　大野班会議　檜山行雄

1

治験薬GMPの一般原則

◆ WHO-GMP／ヒト用治験薬ガイドライン
◆ 薬監第70号（平成9年5月20日付）　より

● 被験者の保護

● 当該治験薬の品質の一貫性・同等性と市販製品への一貫性・同等性

● 治験の信頼性保証

◎ 文書化

⇒ 上記3項目の手順を推進・管理するための手法であり、状況証拠・物的証拠を示す方法

2

市販製品への一貫性・同等性

Phase 0（MD、探索的治験；開発候補の選択？）

Phase I（安全性、薬物動態）

目標用量付近ではPhase II治験への、最高用量に関する知識は市販製品への一貫性が求められる。バッチ内の均一性が求められる。

Phase II（有効性の確認、示適用量の決定）

Phase III治験薬への一貫性・高い類似性が求められる

Phase III（有効性の評価、副作用の評価）

市販製品との同等性・同一性が求められる。

バッチ内の均一性に加えバッチ間の同等性が求められる。

3

治験薬GMPの一般原則

◆ WHO-GMP／ヒト用治験薬ガイドライン

◆ 薬監第70号（平成9年5月20日付）　より

● 被験者の保護

⇒ 開発段階に拘らず、全ての段階で最重要視されるべきもの

● 当該治験薬の品質の一貫性・同等性と市販製品への一貫性・同等性

⇒ Phase 0においてまで求められるものか否かは疑問

● 治験の信頼性保証

⇒ 品質データ（製造記録および品質管理記録）と連動

◎ 文書化

⇒ 上記3項目の手順を推進・管理するための手法であり、状況証拠・物的証拠を示す方法

4

開発段階の品質保証として考えられること

●治験薬GMPの一般原則は研究・開発といった目的に拘らず適用できる

●被験者の保護が何よりも優先される

●有効性・安全性のデータの信頼性は、用いる開発品の品質データに依存

●ただ、品質の一貫性・同等性については、探索的臨床試験・MD試験における目的を考慮すると必要性は疑問

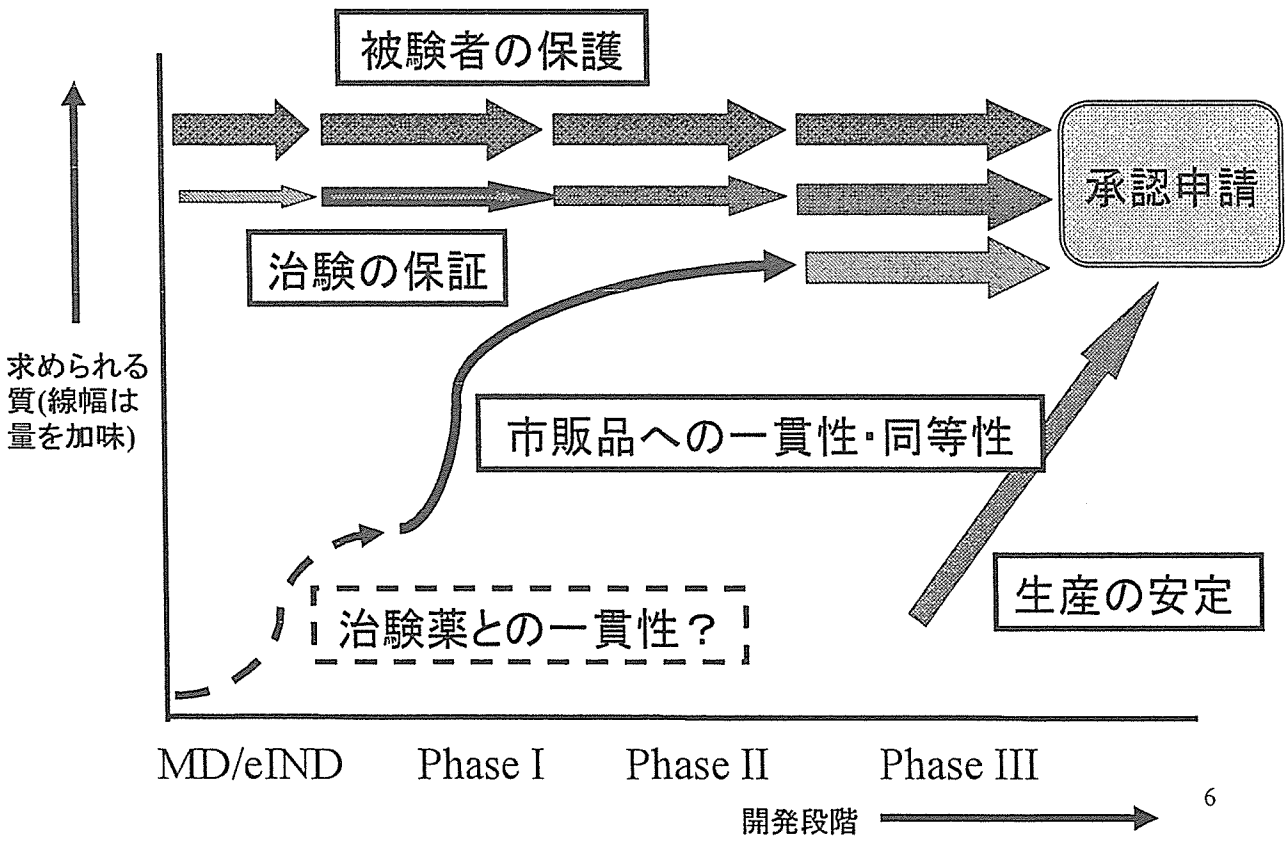
●原薬の投与量と共に不純物量・プロフィールへの注意は重要（安全性の基準）

●投与形態、事業所の複雑性によっては、開発段階に拘らず注意すべき事項あり

⇒たとえば、注射剤の無菌性保証、専用施設か複数製品製造かなど

5

開発段階に応じた各原則の適用レベル



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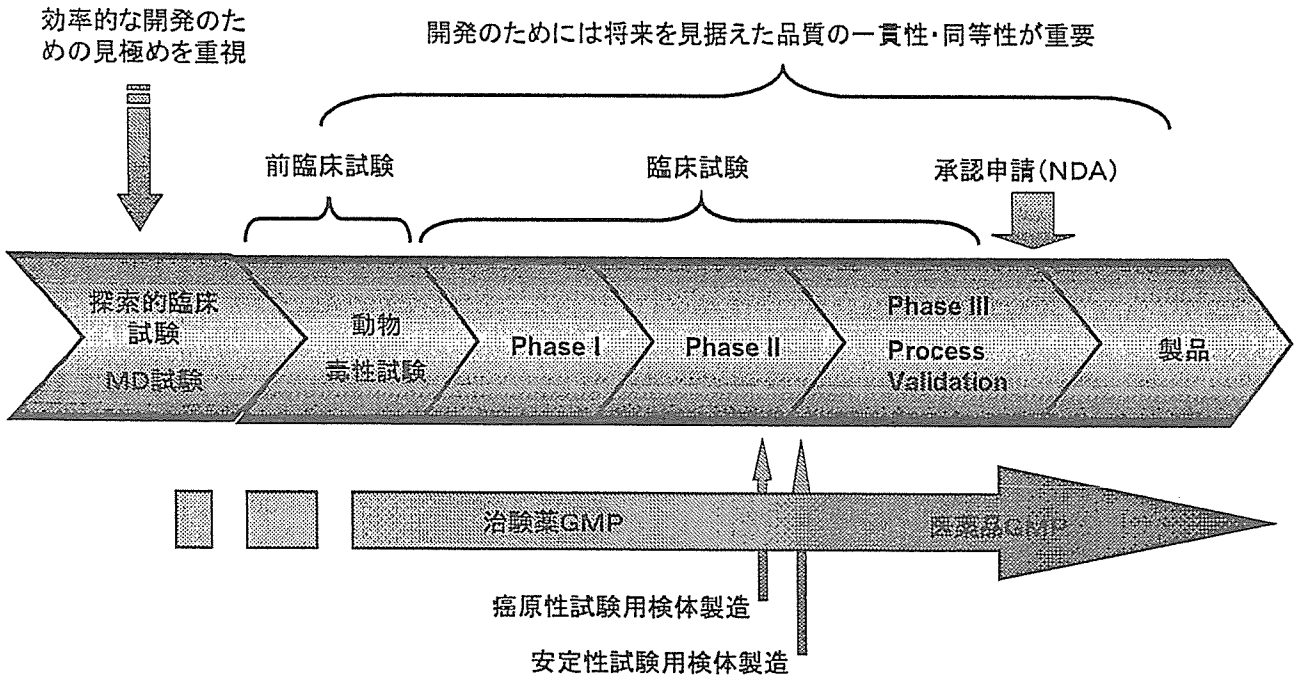
研究 & 開発(今後の図式として)



7

開発段階の品質保証について
ー あるべき姿、現状と課題の要約 ー

【あるべき姿】

●開発段階の品質保証(治験薬GMPを含む)は開発段階の状況に応じて適切に行うことが効率的・効果的である

【現状】

●現行治験薬GMP通知は、前期治験に対し過剰な要求をする一方で、後期治験に対しては不十分なところがある(探索的臨床試験は想定外)

【課題】

●MD試験を含む探索的臨床試験においても最低限度の品質要件は必要である

●国際調和も考慮した上で開発段階に応じた柔軟な品質保証が必要である

●そのためには現行治験薬GMPの改訂も視野に入れる必要がある

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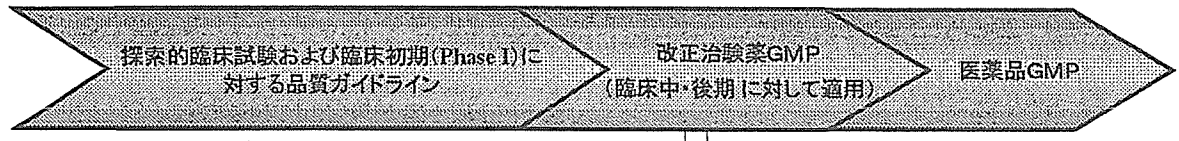
開発段階の品質保証：治験薬GMP＆ガイドライン

【案1】

【案2】

【案3】



《注1》医薬品GMP＝GMP省令＋薬局等構造設備規則
《注2》治験薬GMPについては、医薬品GMPの追補というパターンも考慮
《注3》改正治験薬GMPおよび臨床初期品質ガイドラインの内容(Minimum Requirements)については、今後検討
《注4》具体的運用や解釈については、必要に応じて、Q&A等による補足も考慮

9

行動計画

1　治験薬GMPの改定の基本方針の確認および作業

バリデーションに代えベリフィケーションの概念を入れる－過大要求の是正；　一貫性

品質部門の関わり方、組織要求並びに文書要求の検討；治験保証の程度

開発段階に拘わらず必要な管理は新たに入れる；例えば無菌操作

2　上記基本方針に基づいた治験薬GMPを補完する探索的治験における方針を構築し、ガイドラインを作成する

下線部が今年度の活動

10

治験薬の品質確保指針作成の作業について

2007年3月13日　大野班会議　檜山行雄

1

行動計画

1　治験薬GMPの改定の基本方針の確認および作業

バリデーションに代えベリフィケーションの概念を入れる一過大要求の是正；　一貫性

品質部門の関わり方、組織要求並びに文書要求の検討；治験保証の程度

開発段階に拘わらず必要な管理は新たに入れる；例えば無菌操作

2　上記基本方針に基づいた治験薬GMPを補完する探索的治験における方針を構築し、ガイドラインを作成する

下線部が今年度の活動

2

具体的な作業手順

1　薬発第480号各条へのコメントと代案並びに論拠を挙げる

MD治験、探索的治験、後期治験それぞれの切り口から

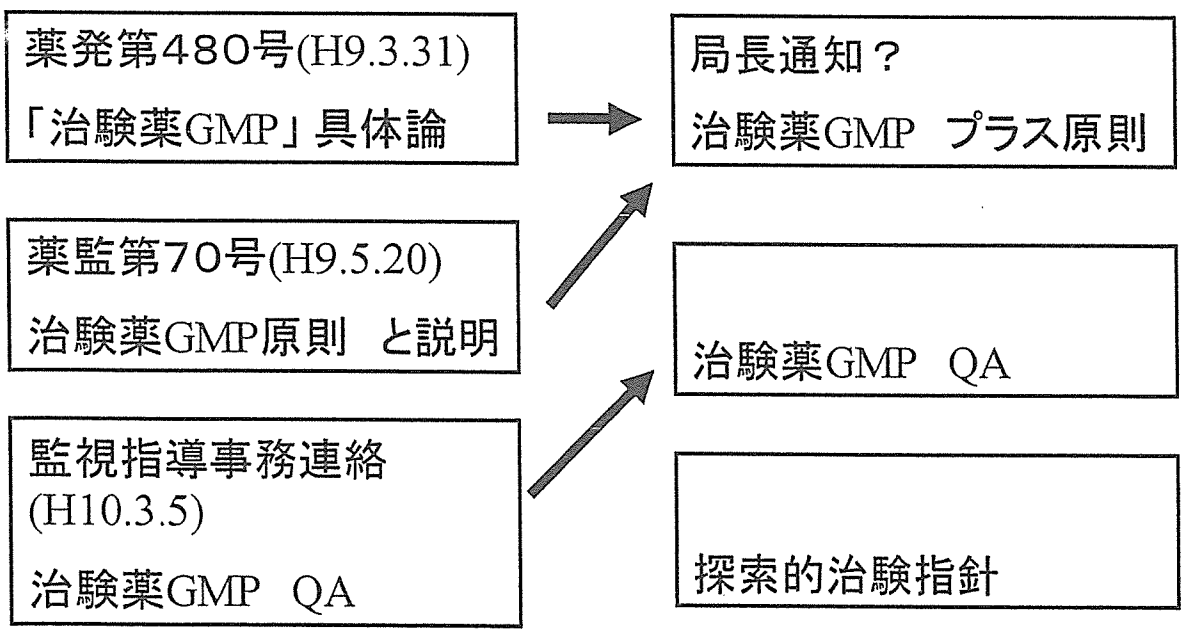
2　1の上位概念を18年度にすべて挙げる

3　治験薬GMP通知の改定作業

MD治験、探索的治験の論点を可能な限り通知本体に包含したい
通知本体で包含できない点（MD、探索に限らず出てくる）はQAなり指針でカバーする

1の重要点と2は18年度、3は次年度

3



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添付資料　4-d 研究班全体会議配布資料
Version 2
2007年3月12日

探索的臨床試験における被験物質の品質確保について
― 探索的臨床試験における品質保証の方針 ―

大野班・品質分科会

《注》下記、治験薬のGMPと記したものは、治験に用いる治験薬のGMP全般(WHOガイドラインおよび薬監第70号（平成9年5月20日付）にある原則に基づく品質・製造管理手法）を意味し、「治験薬GMP」と記したものは、平成9年3月31日付／薬発第480号そのもの（具体的手法）を意味しております。

1．探索的臨床試験について

1－5．被験物質（治験薬）の品質確保について

1）治験薬の GMP の原則の遵守

治験薬は、WHO-GMP／ヒト用治験薬ガイドラインおよび薬監第70号（平成9年5月20日付）を遵守した品質のものである必要がある。

● 被験者の保護
開発段階に拘らず、全ての段階で最優先・最重要視されるべきものである。

● 治験の信頼性保証
治験データおよび将来の申請データの信頼性を保証するためにも、品質データとの連動は欠くべからざるものである。

● 当該治験薬の品質の均一性と市販製品への一貫性・同等性
有効性および安全性の担保、そして将来の市販製品の保証のために、品質の均一性・一貫性・同等性は極めて重要なものである。

◎ 文書化
上記3項目の手順を推進・管理するための手法であり、状況証拠・物的証拠を示す唯一の方法である。

2）現状の問題点

現行の「治験薬 GMP」（平成9年3月31日付／薬発第480号）においては、以下の問題点がある。

① 開発段階の全てのフェーズに対して同一の要件が求められている。
- 前期治験に対しては、過剰な要求をしており、現実的でない。
- 後期治験に対しては、医薬品 GMP への継続としての目的が反映されておらず、不充分なところがある。

② 探索的臨床試験を想定した内容になっておらず、現行「治験薬 GMP」をそのまま適用するのは不適切であり、現実に対応不能である。

③ 放射性治験薬については、その取り扱いに対する留意事項や施設等、全く言及されておらず、MD試験への適用ができない。

3）検討すべき課題

現行「治験薬GMP」の改正も視野に入れて、MD試験も含めた探索的臨床試験に使用する被験物質の品質保証を検討するにあたって留意すべき事項としては、以下のものがある。

①探索的臨床試験（MD試験を含む）においても、被験者の保護を最優先して考えるならば、最低限度の品質要件は必要である。

②国際調和を意識した上で、以降の治験（Phase 1～Phase 3）との目的の相違も考慮した、開発段階に応じた柔軟な品質保証が必要である。

③放射性の検体（被験物質調製に用いる物質を含む）の取り扱いやその施設については、現実的対応が考慮されたものである必要がある。

4）今後の対応のために

WHO-GMP／ヒト用治験薬ガイドラインおよび薬監第70号（平成9年5月20日付）の治験薬に対する一般原則を理解した上で、探索的臨床試験の目的と意義を踏まえ、倫理的側面と科学的側面に重点を置いた現実的運用の可能な指針が望まれる。

● 被験者の保護 ： 倫理的側面
未知のものをヒトに投与する以上、何よりも最優先・最重要視されるべきものであることを理解する。

● 臨床試験の信頼性保証 ： 科学的側面
将来の申請データへの係わりの有無に拘らず、当該被験物質から得られた臨床試験のデータが科学的に妥当なものとして保証し得るレベルのものである必要があることを理解する。

◎ 文書化 ： 状況を証明する手段（物的証拠）
「被験者の保護」「臨床試験の信頼性保証」の手順を推進・管理するための手法であり、状況を示す唯一の物的証拠であることを理解する。

○ 将来の治験薬の品質の均質性と市販製品への一貫性・同等性： 物性的側面
近い将来の第1相臨床試験との品質上の相関を求めるものではないが、当該被験物質が将来の市販製品に向けて、以降の開発においては均質性・一貫性・同等性が問われるものであることを理解する。

以上

EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market : management & legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Brussels,
F2/BL D(2003)

Revision 1

VOLUME 4

Good manufacturing practices

ANNEX 13

Manufacture of investigational medicinal products

JULY 2003

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ANNEX 13 REVISION 1

PRINCIPLE

Investigational medicinal products should be produced in accordance with the principles and the detailed guidelines of Good Manufacturing Practice for Medicinal Products (The Rules Governing Medicinal Products in The European Community, Volume IV). Other guidelines published by the European Commission should be taken into account where relevant and as appropriate to the stage of development of the product. Procedures need to be flexible to provide for changes as knowledge of the process increases, and appropriate to the stage of development of the product.

In clinical trials there may be added risk to participating subjects compared to patients treated with marketed products. The application of GMP to the manufacture of investigational medicinal products is intended to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture. Equally, it is intended to ensure that there is consistency between batches of the same investigational medicinal product used in the same or different clinical trials, and that changes during the development of an investigational medicinal product are adequately documented and justified.

The production of investigational medicinal products involves added complexity in comparison to marketed products by virtue of the lack of fixed routines, variety of clinical trial designs, consequent packaging designs, the need, often, for randomisation and blinding and increased risk of product cross-contamination and mix up. Furthermore, there may be incomplete knowledge of the potency and toxicity of the product and a lack of full process validation, or, marketed products may be used which have been re-packaged or modified in some way.

These challenges require personnel with a thorough understanding of, and training in, the application of GMP to investigational medicinal products. Co-operation is required with trial sponsors who undertake the ultimate responsibility for all aspects of the clinical trial including the quality of investigational medicinal products.

The increased complexity in manufacturing operations requires a highly effective quality system.

The annex also includes guidance on ordering, shipping, and returning clinical supplies, which are at the interface with, and complementary to, guidelines on Good Clinical Practice.

NOTE

Products other than the test product, placebo or comparator may be supplied to subjects participating in a trial. Such products may be used as support or escape medication for preventative, diagnostic or therapeutic reasons and/or needed to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the protocol to induce a physiological response. These products do not fall within the definition of investigational medicinal products and may be supplied by the sponsor, or the investigator. The sponsor should ensure that they are in accordance with the notification/request for authorisation to conduct the trial and that they are of appropriate quality for the purposes of the trial taking into account the source of the materials, whether or not they are the subject of a marketing authorisation and whether they have been repackaged. The advice and involvement of a Qualified Person is recommended in this task.

GLOSSARY

Blinding

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s). In relation to an investigational medicinal product, blinding shall mean the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor. Unblinding shall mean the disclosure of the identity of blinded products.

Clinical trial

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of one or more investigational medicinal product(s) with the object of ascertaining its/their safety and/or efficacy.

Comparator product

An investigational or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial.

Investigational medicinal product

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

Immediate packaging

The container or other form of packaging immediately in contact with the medicinal or investigational medicinal product.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Manufacturer/importer of Investigational Medicinal Products

Any holder of the authorisation to manufacture/import referred to in Article 13.1 of Directive 2001/20/EC.

Order

Instruction to process, package and/or ship a certain number of units of investigational medicinal product(s).

Outer packaging

The packaging into which the immediate container is placed.

Product Specification File
A reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product.

Randomisation

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Randomisation Code

A listing in which the treatment assigned to each subject from the randomisation process is identified.

Shipping
The operation of packaging for shipment and sending of ordered medicinal products for clinical trials.

Sponsor
An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

QUALITY MANAGEMENT

1. The Quality System, designed, set up and verified by the manufacturer or importer, should be described in written procedures available to the sponsor, taking into account the GMP principles and guidelines applicable to investigational medicinal products.

2 The product specifications and manufacturing instructions may be changed during development but full control and traceability of the changes should be maintained.

PERSONNEL

3. All personnel involved with investigational medicinal products should be appropriately trained in the requirements specific to these types of product.

4. The Qualified Person should in particular be responsible for ensuring that there are systems in place that meet the requirements of this Annex and should therefore have a broad knowledge of pharmaceutical development and clinical trial processes. Guidance for the Qualified Person in connection with the certification of investigational medicinal products is given in paragraphs 38 to 41.

PREMISES AND EQUIPMENT

5. The toxicity, potency and sensitising potential may not be fully understood for investigational medicinal products and this reinforces the need to minimise all risks of cross-contamination. The design of equipment and premises, inspection / test methods and acceptance limits to be used after cleaning should reflect the nature of these risks. Consideration should be given to

campaign working where appropriate. Account should be taken of the solubility of the product in decisions about the choice of cleaning solvent.

DOCUMENTATION

Specifications and instructions

6. Specifications (for starting materials, primary packaging materials, intermediate, bulk products and finished products), manufacturing formulae and processing and packaging instructions should be as comprehensive as possible given the current state of knowledge. They should be periodically re-assessed during development and updated as necessary. Each new version should take into account the latest data, current technology used, regulatory and pharmacopoeial requirements, and should allow traceability to the previous document. Any changes should be carried out according to a written procedure, which should address any implications for product quality such as stability and bio equivalence.

7. Rationales for changes should be recorded and the consequences of a change on product quality and on any on-going clinical trials should be investigated and documented.

Order

8. The order should request the processing and/or packaging of a certain number of units and/or their shipping and be given by or on behalf of the sponsor to the manufacturer. It should be in writing (though it may be transmitted by electronic means), and precise enough to avoid any ambiguity. It should be formally authorised and refer to the Product Specification File and the relevant clinical trial protocol as appropriate.

Product Specification File

9. The Product Specification File (see glossary) should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions. It should include, or refer to, the following documents:
   - Specifications and analytical methods for starting materials, packaging materials, intermediate, bulk and finished product.
   - Manufacturing methods.
   - In-process testing and methods.
   - Approved label copy.
   - Relevant clinical trial protocols and randomisation codes, as appropriate.
   - Relevant technical agreements with contract givers, as appropriate.
   - Stability data.
   - Storage and shipment conditions.

The above listing is not intended to be exclusive or exhaustive. The contents will vary depending on the product and stage of development. The information should form the basis for assessment of the suitability for certification and release of a particular batch by the Qualified Person and should therefore be accessible to him/her. Where different manufacturing steps are carried out at different locations under the responsibility of different Qualified Persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.

Manufacturing Formulae and Processing Instructions

10. For every manufacturing operation or supply there should be clear and adequate written instructions and written records. Where an operation is not repetitive it may not be necessary to produce Master Formulae and Processing Instructions. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture once the marketing authorisation is granted.

11. The information in the Product Specification File should be used to produce the detailed written instructions on processing, packaging, quality control testing, storage conditions and shipping.

Packaging Instructions

12. Investigational medicinal products are normally packed in an individual way for each subject included in the clinical trial. The number of units to be packaged should be specified prior to the start of the packaging operations, including units necessary for carrying out quality control and any retention samples to be kept. Sufficient reconciliations should take place to ensure the correct quantity of each product required has been accounted for at each stage of processing.

Processing, testing and packaging batch records

13. Batch records should be kept in sufficient detail for the sequence of operations to be accurately determined. These records should contain any relevant remarks which justify the procedures used and any changes made, enhance knowledge of the product and develop the manufacturing operations.

14. Batch manufacturing records should be retained at least for the periods specified in Directive 91/356 as amended for investigational medicinal products.

PRODUCTION

Packaging materials

15. Specifications and quality control checks should include measures to guard against unintentional unblinding due to changes in appearance between different batches of packaging materials.

Manufacturing operations

16. During development critical parameters should be identified and in-process controls primarily used to control the process. Provisional production parameters and in-process controls may be deduced from prior experience, including that gained from earlier development work. Careful consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them continually to the experience gained in production. Parameters identified and controlled should be justifiable based on knowledge available at the time.

17. Production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production but premises and equipment are expected to be validated. For sterile products, the validation of sterilising processes should be of the same standard as for products authorised for marketing.

Likewise, when required, virus inactivation/removal and that of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived products, by following the scientific principles and techniques defined in the available guidance in this area.

18. Validation of aseptic processes presents special problems when the batch size is small; in these cases the number of units filled may be the maximum number filled in production. If practicable, and otherwise consistent with simulating the process, a larger number of units should be filled with media to provide greater confidence in the results obtained. Filling and sealing is often a manual or semi-automated operation presenting great challenges to sterility so enhanced attention should be given to operator training, and validating the aseptic technique of individual operators.

Principles applicable to comparator product

19. If a product is modified, data should be available (e.g. stability, comparative dissolution, bioavailability) to demonstrate that these changes do not significantly alter the original quality characteristics of the product.

20. The expiry date stated for the comparator product in its original packaging might not be applicable to the product where it has been repackaged in a different container that may not offer equivalent protection, or be compatible with the product. A suitable use-by date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the article may be subjected, should be determined by or on behalf of the sponsor. Such a date should be justified and must not be later than the expiry date of the original package. There should be compatibility of expiry dating and clinical trial duration.

Blinding operations

21. Where products are blinded, systems should be in place to ensure that the blind is achieved and maintained while allowing for identification of "blinded" products when necessary, including the batch numbers of the products before the blinding operation. Rapid identification of product should also be possible in an emergency.

Randomisation code

22. Procedures should describe the generation, security, distribution, handling and retention of any randomisation code used for packaging investigational products, and code-break mechanisms. Appropriate records should be maintained.

Packaging

23. During packaging of investigational medicinal products, it may be necessary to handle different products on the same packaging line at the same time. The risk of product mix up must be minimised by using appropriate procedures and/or, specialised equipment as appropriate and relevant staff training.

24. Packaging and labelling of investigational medicinal products are likely to be more complex and more liable to errors (which are also harder to detect) than for marketed

products, particularly when "blinded" products with similar appearance are used. Precautions against mis-labelling such as label reconciliation, line clearance, in-process control checks by appropriately trained staff should accordingly be intensified.

25. The packaging must ensure that the investigational medicinal product remains in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.

Labelling

26. Table 1 summarises the contents of articles 26-30 that follow. Labelling should comply with the requirements of Directive 91/356 as amended for Investigational Medicinal Products. The following information should be included on labels, unless its absence can be justified, e.g. use of a centralised electronic randomisation system:

(a) name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding);
(b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;
(c) the batch and/or code number to identify the contents and packaging operation;
(d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
(e) the trial subject identification number/treatment number and where relevant, the visit number;
(f) the name of the investigator (if not included in (a) or (d));
(g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product);
(h) "For clinical trial use only" or similar wording;
(i) the storage conditions;
(j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.
(k) "keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.

27. The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times.

28. Particulars should appear in the official language(s) of the country in which the investigational medicinal product is to be used. The particulars listed in Article 26 should appear on the immediate container and on the outer packaging (except for immediate containers in the cases described in Articles 29 and 30). The requirements with respect to the contents of the label on the immediate container and outer packaging are summarised in table 1. Other languages may be included.

29. When the product is to be provided to the trial subject or the person administering the medication within an immediate container together with outer packaging that is intended to remain together, and the outer packaging carries the particulars listed in paragraph 26, the following information shall be included on the label of the immediate container (or any sealed dosing device that contains the immediate container):

a) name of sponsor, contract research organisation or investigator;
b) pharmaceutical dosage form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and in the case of open label trials, the name/identifier and strength/potency;
c) batch and/or code number to identify the contents and packaging operation;
d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
e) the trial subject identification number/treatment number and where relevant, the visit number.

30. If the immediate container takes the form of blister packs or small units such as ampoules on which the particulars required in paragraph 26 cannot be displayed, outer packaging should be provided bearing a label with those particulars. The immediate container should nevertheless contain the following:

a) name of sponsor, contract research organisation or investigator;
b) route of administration (may be excluded for oral solid dose forms) and in the case of open label trials, the name/identifier and strength/potency;
c) batch and/or code number to identify the contents and packaging operation;
d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
e) the trial subject identification number/treatment number and where relevant, the visit number;

31. Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings and/or handling instructions may be displayed.

32. For clinical trials with the characteristics identified in Article 14 of Directive 2001/20/EC, the following particulars should be added to the original container but should not obscure the original labelling:
i) name of sponsor, contract research organisation or investigator;
ii) trial reference code allowing identification of the trial site, investigator and trial subject.

33. If it becomes necessary to change the use-by date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new use-by date and repeat the batch number. It may be superimposed on the old use-by date, but for quality control reasons, not on the original batch number. This operation should be performed at an appropriately authorised manufacturing site. However, when justified, it may be performed at the investigational site by or under the supervision of the clinical trial site pharmacist, or other health care professional in accordance with national regulations. Where this is not possible, it may be performed by the clinical trial monitor(s) who should be appropriately trained. The operation should be performed in accordance with GMP principles, specific and standard operating procedures and under contract, if applicable, and should be checked by a

second person. This additional labelling should be properly documented in both the trial documentation and in the batch records.

QUALITY CONTROL

34. As processes may not be standardised or fully validated, testing takes on more importance in ensuring that each batch meets its specification.

35. Quality control should be performed in accordance with the Product Specification File and in accordance with the information notified pursuant to Article 9(2) of Directive 2001/20/EC. Verification of the effectiveness of blinding should be performed and recorded.

36. Samples of each batch of investigational medicinal product, including blinded product should be retained for the periods specified in Directive 91/356 as amended for investigational medicinal products.

37. Consideration should be given to retaining samples from each packaging run/trial period until the clinical report has been prepared to enable confirmation of product identity in the event of, and as part of an investigation into inconsistent trial results.

RELEASE OF BATCHES

38. Release of investigational medicinal products (see paragraph 43) should not occur until after the Qualified Person has certified that the requirements of Article 13.3 of Directive 2001/20/EC have been met (see paragraph 39). The Qualified Person should take into account the elements listed in paragraph 40 as appropriate.

39. The duties of the Qualified Person in relation to investigational medicinal products are affected by the different circumstances that can arise and are referred to below. Table 2 summarises the elements that need to be considered for the most common circumstances:

a)i) Product manufactured within EU but not subject to an EU marketing authorisation: the duties are laid down in article 13.3(a) of Directive 2001/20/EC.

a)ii) Product sourced from the open market within EU in accordance with Article 80(b) of Directive 2001/83/EC and subject to an EU marketing authorisation, regardless of manufacturing origin: the duties are as described above, however, the scope of certification can be limited to assuring that the products are in accordance with the notification/request for authorisation to conduct the trial and any subsequent processing for the purpose of blinding, trial-specific packaging and labelling. The Product Specification File will be similarly restricted in scope (see 9).

b) Product imported directly from a 3rd country: the duties are laid down in article 13.3(b) of Directive 2001/20/EC. Where investigational medicinal products are imported from a 3rd country and they are subject to arrangements concluded between the Community and that country, such as a Mutual Recognition Agreement (MRA), equivalent standards of Good Manufacturing Practice apply provided any such agreement is relevant to the product in question. In the absence of an MRA, the Qualified Person should determine that equivalent standards of Good Manufacturing Practice apply through knowledge of the quality system employed at the manufacturer. This knowledge is normally acquired through participation in audit of the manufacturer's quality systems. In either case,