Date of implementation: 1 March 2010

Introduction:
The holder of a Certificate of suitability shall inform the EDQM of any change to the information in the certification dossier by sending an application form and all necessary documents demonstrating that the conditions laid down in the present guideline are met.

Classification of changes
The changes have been classified in three categories (notification/minor/major) depending on the potential impact of the change on the quality of the final substance. These three categories are based on those (IA-IAIN/IB/II) of the Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisation for medicinal products for human use and veterinary medicinal products.

Any change not classified as a notification or a major change should be classified as a minor change except in the following cases where a new application should be submitted:

- addition of a new route of synthesis and/or a new manufacturing site where the specifications of the final substance are different from the one already approved

- transfer to a new holder that is not the same legal entity as the approved one, where the transfer does not occur because of a merger or because the company is sold, and where the manufacturer does not take out the Certificate of suitability in their own name.

The changes related to Ph. Eur. monograph revisions or any other regulatory requirements are treated separately and generally initiated by the EDQM.

执行日期：2010 年 3 月 1 日

介绍：
欧洲药典适用性证书持有人必须向 EDQM 报告所有与申报文件有关的变更，申报时应填写申请表格和所有必要的资料，证明变更符合现行指南的规定。
变更分类

根据变更对最终产品可能产生的影响程度，变更分为三类（通知/微小/重大）。
分类原则是根据 EC 法规 1234/2008 (IA-IAIN/IB/II)：EC 成员国审核人用和兽用制剂销售许可证变更规定
所有未划为通知或者重大变更的变更都是微小变更，但以下情形必须按新证书申请办理：

- 增加新合成途径或新生产场地，而且成品质量标准发生变化。

- 持有人转让，新持有人与现行法人不同，这种转让不是公司合并、出售的结果，生产厂也没有以自己名义获取原有证书。

欧洲药典修订或其它法规要求而产生的变更另论，通常由 EDQM 发起。

Documentation to be provided

For any revision the documentation should consist of:
- a cover letter
- the application form, duly filled and listing all the changes applied for
- a description of each change together with a justification
- data showing, when applicable, that the conditions have been met
- update of the relevant section(s) of the dossier (presented in EU-CTD format).
- the specific documents described below for each change and supporting the change
- supportive information, including comparative data with the previous version of the dossier (in tabular format), showing the approved and the proposed section and highlighting the changes

Consequential changes should be identified and the relation between the changes should be described.

Each time batch data are needed:
- they should be in accordance with the specifications of the current Ph. Eur. monograph and when relevant with the additional requirements included in the Certificate of suitability
- the manufacturing site, the manufacturing date and the size of the batches should be specified.
- quantitative results should be presented numerically (i.e. not in general terms such as “complies”) and with the appropriate number of decimal places.

需要申报的文件

所有变更的申报文件必须包括以下内容：
- 附函
- 申请表，列出申请的变更
- 变更内容并说明变更的合理性
- 若适用的的话，表明符合条件的数据
- 更新申报文件相关的章节（按 EU-CTD 格式）
- 下述各种变动所要求的具体文件
- 支持性信息，包括与原版本的对比数据（以表格格式），表明原内容及现内容，强调变更应该识别间接的变更，并描述变更之间的关系。

所有变更都需要申报批分析数据：
- 而且必须现行欧洲药典标准、以及 CEP 证书附加的有关要求。
- 必须说明生产场地、生产日期和生产批量。
- 应以数字形式表示定量结果（即：不得笼统表达为“合格”等），数位应合理。

The changes are presented in five sections:
- Notifications (N and T)
- Typical minor revisions for Certificates of suitability for chemical purity and microbiological quality or for TSE Certificates of suitability

- Major revisions (MAJ)
- Renewal
- Transfer of holdership

Editorial changes should not be submitted as separate variations but should be reported at the same time as changes concerning the respective part of the dossier. In any case, a declaration should be provided that the content of the concerned part of the dossier has not been changed by the editorial changes (except for the change itself).

以下分五节讨论各种变更情况：

通知（N 和 T）

化学纯度和微生物质量的 CEP 证书或 TSE 证书的典型微小变更

重大变更（MAJ）

更新

证书持有人转让

文字性变更不应作为单独的变更提交，但当文件相关部分变更时应当同时报告。不管怎么样，应该申明：除了变更本身之外，文件相关部分的内容没有因文字性的变更而发生变更。

NOTIFICATIONS (IN/AN)

Notifications are split into immediate notifications and notifications with annual reporting.

1. Immediate notifications (IN):

IN1) Change in the name and/or address of the certificate holder of the final substance (former N1)

Conditions:

- the certificate holder shall remain the same legal entity (except where the company is sold or in case of a merger).

Specific Documentation:

- a formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or the new address is mentioned
- all updated declarations (annexes to the application form).

通知（（IN/AN）

通知分为立即通知和年度报告的通知

1. 立即通知 IN

IN1 原料药证书持有人名称或地址变更 （以前的 N1）

条件：

- 证书持有人法人地位不变（公司出让或被兼并除外）。

文件要求：

- 官方出具（如：商会）的有关新名称和新地址的正式文件
- 所有更新的声明（见申请表附录）

IN2) Change in the name and/or address of the manufacturing site for the final substance (former N2)

Conditions:

- the location of the manufacturing site shall remain the same.

Specific Documentation:
- a formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or the new address is mentioned
- updated declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected.

IN2 原料药生产场所名称或地址变更 （以前的 N2）
条件：生产场所具体位置应保持不变。
文件要求：
- 官方出具（如：商会）的有关新名称和新地址的正式文件
- 更新的声明：按申报文件和 GMP 法规组织生产及愿意接受检查的声明

IN3) Deletion of any manufacturing site for the final substance (former N3)
Conditions:
- the deletion should not be due to critical deficiencies concerning manufacturing.
Specific Documentation:
- the justification of the deletion.
IN3 原料药生产场地的取消（以前的 N3）
条件：取消不应该是由于与生产有关的严重缺陷
文件要求：证明取消的合理性。

IN4) Change or addition of a manufacturer of a starting material or intermediate used in the manufacturing process of the final substance when the proposed manufacturer is part of the same group as the currently approved manufacturer
Conditions:
- the specifications and the route of synthesis (including In-Process Controls, methods of analysis of all materials used) of the concerned material are identical to those already approved
- the final substance is not a biological substance or a sterile substance.
Specific Documentation:
- a declaration from the holder of the Certificate of suitability that the specifications of the final substance are the same as those already approved
- a declaration from the holder of the Certificate of suitability that the synthetic route (or in case of herbal material, where appropriate, the method of preparation, geographical source and production), the specifications and the quality control procedures of the starting material or intermediate are the same as those already approved
- a list of approved and proposed sites
- batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the final substance from the approved and proposed sites.

IN4 变更或增加原料药生产工艺过程中所使用的起始物料或中间体生产厂家，新厂家与原厂家同属一个集团
条件
- 相关物料的质量标准和合成路线（包括中控、所有原料的分析方法）与已批准的相同
- 原料药不是生物制品或无菌制品

文件要求：
- CEP 证书持有者申明原料药的质量标准与已批准的一致
- CEP 证书持有者申明起始物料或中间体的合成路线（或当原料为草药时，其制备方法，地理来源和制造）、质量标准和检测方法与已批准的一致
- 新旧地址的清单
- 新旧地址至少两批（至少为中试批次）原料药的批分析数据（对比表格）。

IN5) Change or addition of a manufacturing site/workshop for the final substance when the proposed manufacturer is part of the same group as the currently approved manufacturer

Conditions:
- the specifications of the final substance (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved
- the final substance is not a biological substance or a sterile substance.
Specific Documentation:
- a declaration from the holder of the Certificate of suitability that the synthetic route (or in case of herbal material, where appropriate the method of preparation, geographical source and production), quality control procedures and specifications of the final substance are the same as those already approved
- a list of approved and proposed sites
- batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the final substance from the approved and proposed sites
- updated declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected for the new site.

IN5 变更或增加原料药的生产地址/车间，新厂家与原厂家同属一个集团

条件
- 原料药的质量标准（包括中控、所有原料的分析方法）和制备方法（包括批量）及详细的合成路线与已批准的相同
- 原料药不是生物制品或无菌制品
文件要求：
- CEP 证书持有者申明原料药的合成路线（或当原料为草药时，其制备方法，地理来源和制造）、质量标准和检测方法与已批准的一致
-新旧地址的清单
-新旧地址至少两批（至少为中试批次）原料药批分析数据（对比表格）
- 更新的声明：按申报文件和 GMP 法规组织生产及愿意接受检查的声明

IN6) Tightening of the specification limits for the final substance (former N8)
Conditions:
- the change does not result from unexpected events arising during manufacture
- any change should be within the range of currently approved limits
- the test procedure remains the same, or changes in the test procedure are minor.

Specific Documentation:
- comparative table of approved and proposed specifications.

IN6) 提高成品质量标准（以前的 N8）

条件:
- 该变动不是生产过程的异常引起
- 所有变动必须符合现行已经批准的质量标准范围
- 分析方法不变或微小变化

文件要求
- 变动前后质量标准对照表

IN7) Minor changes to a test procedure for the final substance. Editorial changes to a method description annexed to a certificate of suitability (former N7)

Conditions:
- appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure
- there have been no changes of the total impurity limits; no new unqualified impurities are detected
- the method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method)
- the test method is not a biological method, or a method using a biological reagent for a biological substance (does not include standard pharmacopoeial microbiological methods).

Specific Documentation:
- updated description of the method in a format to be appended to the certificate of suitability
- amendment of the relevant section(s) of the dossier, including description of the analytical method, summary of validation data,
- comparative validation results, or if justified comparative analysis results showing that the approved test and the proposed one are equivalent.

IN7) 成品检验方法微小变动。CEP 证书规定方法的表述形式变动。（以前的 N7）

条件:
- 已按有关指南要求进行适当的验证研究，证明更新的检验方法至少等同于原方法
- 总杂质限度不变，未检出新杂质
- 分析方法本身不变(如：柱长或柱温改变，但柱子类别或方法不变);
- 检测方法不是生物方法或生物产品使用生物试剂的方法（不包括药典中标准的微生物方法）

文件要求
- 更新后的方法描述，表述应符合 CEP 证书附件方法格式
- 文件相关部分的修订，包括分析方法的描述，验证数据总结等
- 验证结果对比，或仅对比检测结果表明新方法与原方法等同

IN8) Addition of a specification parameter for the final substance

Conditions:
- the change does not result from unexpected events arising during manufacture
- any new test method does not concern a novel non-standard technique or a standard technique used in a novel way
- the test method is not a biological method or a method using a biological reagent for a biological

substance (does not include standard pharmacopoeia microbiological methods)
- the change does not concern a genotoxic impurity

Specific Documentation:
- comparative table of approved and proposed specifications
- details of any new analytical method and validation data, where relevant
- batch analysis data on two production batches of the relevant substance for all specification parameters.

IN8) 增加原料药标准的参数
条件
- 该变动不是生产过程的异常引起
- 任何新的检测方法不涉及新的非标准技术或以新方式使用的标准技术
- 检测方法不是生物方法或生物产品使用生物试剂的方法（不包括药典中标准的微生物方法）
- 变更不涉及基因毒性杂质
文件要求
- 变动前后质量标准对照表
- 若有，任何详细的新的检测方法和验证数据
- 包括相关原料药所有规格参数的两批正式生产的批检验数据

IN9) Removal/reduction of the re-test period from the Certificate of suitability / change to more restrictive storage conditions (former N11)
Conditions:
- the change should not be the result of unexpected events arising during manufacture or because of stability concerns
Specific Documentation:
- the justification of the removal/reduction of the re-test period

IN9 从 CEP 证书上取消/减少再检验日期/贮藏条件变为更严格（以前的 N11）
条件： 该变更不是生产过程的异常或稳定性实验出现问题引起
文件要求：说明取消/减少再检验日期的合理性

IN10) Deletion of an approved change management protocol for design space submission
Conditions:
- the deletion of the approved change management protocol is not a result of unexpected events or out of specification results during the implementation of the change (s) described in the protocol.
Specific Documentation:
- amendment of the relevant section(s) of the dossier

IN10 删除已批准的用于设计空间提交的变更管理方案
条件
- 删除已批准的变更管理方案不是由于异常结果，或在执行该方案所描述的变更过程中引起的 OOS 结果
文件要求：
- 修订文件相关的部分

2. Notification with annual reporting (AN):

AN1) Change in the name and/or address of a manufacturer of a starting material or intermediate used in the manufacture of the final substance

Conditions:

- the location of the manufacturing site shall remain the same

Specific Documentation:

- updated list of manufacturers of starting material/intermediate

2. 年度报告的通知 （AN）

AN1 原料药生产工艺过程中所使用的起始物料或中间体厂家名称和/或地址变更

条件

- 生产地址的地理位置不变

文件要求

-更新的起始物料/中间体厂家清单

AN2) Deletion of a manufacturer of a starting material/intermediate used in the manufacture of the final substance (former N4)

Conditions:

- the deletion should not be due to critical deficiencies concerning manufacturing

Specific Documentation:

- the justification of the deletion
- updated list of manufacturers of starting material/intermediate

AN2 取消原料药生产工艺过程中所使用的中间体/起始物质的生产厂家

条件：取消不应该是由于与生产有关的严重缺陷

文件要求：

-证明取消的合理性

-更新的起始物料/中间体厂家清单

AN3) Change in the code product/reference number and/or in the brand name of the final substance or any material used in its manufacture (former N9)

Condition:

- the change does not regard the quality of the final substance or the concerned material

Specific Documentation:

- approved and proposed code product / reference number / brand name

AN3 原料药或生产过程使用的任一物料的产品代码或索引号或商标名变更（以前的 N9）

条件:

- 变更与原料药质量或相关的物料质量无关

文件要求

- 产品代码、索引号、商标名新旧对照表

AN4) Minor change in the manufacturing process of the final substance (former R1)

Conditions:

- the specifications of the final substance or intermediates are unchanged and there is no adverse

change in qualitative and quantitative impurity profile
- the synthetic route remains the same, i.e. intermediates remain the same and there are no new reagents, catalysts or solvents used in the process. In the case of herbal products, the geographical source and production of the herbal material remain unchanged
- the final substance is not a biological substance.
Specific Documentation:
- batch analysis data (in comparative tabular format) of at least two batches (minimum pilot scale) manufactured according to the currently approved and proposed process.

AN4 原料药生产工艺的微小变化（以前的 R1）
条件:
- 原料药或中间体标准不变，并且定性、定量的杂质概况均没有不利的变化
- 合成途径未变，即：中间体不变，而且工艺中未用到新试剂、催化剂或溶剂。对于植物制剂产品，其地理来源及生产操作不变
- 原料药不是生物制品
文件要求
- 工艺变动前后至少两个批号产品的批分析数据(对比表格) (至少应为中试批)

AN5) Change in batch size of final substance or intermediate up to 10-fold compared to the original batch size (former N5)
Conditions:
- any changes to the manufacturing methods are only those necessitated by scale-up, e.g. use of different-sized equipment
- test results of at least two batches of the final substance complying with the approved specifications should be available for the proposed batch size
- the substance is not a biological substance or a sterile substance
- the change does not affect the reproducibility of the manufacturing process
- the specifications of the final substance/intermediates remain the same
- the currently approved batch size was not approved via a notification
Specific Documentation:
- the batch numbers of the tested batches having the proposed batch size
- approved and proposed batch size
- updated description of the full process specifying the proposed batch size
- a declaration from the certificate holder that the changes to the manufacturing methods are only those necessitated by scale-up, that the change does not adversely affect the reproducibility of the process, and that the specifications of the final substance/intermediates remain the same.

AN5 成品或中间体批量变动，但不超过原批量 10 倍（以前的 N5）
条件
- 生产方法所有变动只与批量放大有关，如：使用不同大小的设备
- 至少有符合已批准质量标准的两个成品批号检验结果（新批量）
- 产品不是生物或无菌产品
- 变更不影响生产工艺的重现性
- 成品/中间体质量标准不变

- 原批量不是经过通知批准的

文件要求

- 新生产批号（新批量）
- 原批准批量和新批量
- 批量变动后，新的工艺描述
- 证书持有者申明：-生产方法所有变动只与批量放大有关；变动不影响生产工艺的重现性；成品/中间体质量标准不变

AN6) Change in batch size of final substance or intermediate: downscaling (former N6)

Conditions:

- any changes to the manufacturing methods are only those necessitated by the downscaling, e.g. use of different-sized equipment
- test results of at least two batches of the final substance complying with the approved specifications should be available for the proposed batch size
- the substance is not a biological substance or a sterile substance
- the change does not affect the reproducibility of the manufacturing process
- the change should not be the result of unexpected events arising during manufacture or because of stability concerns
- the currently approved batch size was not approved via a notification.

Specific Documentation:

- the batch numbers of the tested batches having the proposed batch size
- approved and proposed batch size
- updated description of the full process specifying the proposed batch size
- a declaration from the certificate holder that the changes to the manufacturing methods are only those necessitated by downscaling, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns and that the specifications of the final substance/intermediates remain the same.

AN6 成品或中间体批量变更：变小（以前的 N5）

条件:

- 生产方法所有变动只与批量变小有关，如：使用不同大小的设备
- 至少有符合已批准质量标准的两个成品批号检验结果（新批量）
- 产品不是生物或无菌产品
- 变更不影响生产工艺的重现性
- 该变动原因不是生产过程的异常或由于稳定性有关的问题引起的
- 原批量不是经过通知批准的

文件要求

- 新生产批号（新批量）
- 原批准批量和新批量
- 批量变动后，新工艺的完整描述
- 证书持有者申明：-生产方法所有变动只与批量变小有关；变动不影响生产工艺的重现性，不是生产过程的异常或由于稳定性有关的问题引起的；成品/中间体质量标准不变

AN7) Addition of a new in-process test and limit applied during the manufacture of the final

substance

Conditions:

- the change does not result from unexpected events arising during manufacture
- any new test method does not concern a novel non-standard technique or a standard technique used in a novel way
- the new test method is not a biological method or a method using a biological reagent for a biological substance (does not include standard pharmacopoeial microbiological methods).

Specific Documentation:

- comparative table of approved and proposed in-process tests
- details of any new non-pharmacopoeial analytical method and validation data, where relevant.

AN7) 成品制造增加新的中控检测和限度

条件

-该变动原因不是生产过程的异常引起的
- 任何新的检测方法不涉及新的非标准技术或以新方式使用的标准技术
- 新的检测方法不是生物方法或生物产品使用生物试剂的方法（不包括药典中标准的微生物方法）

文件要求：

- 新旧中控检测对比表
- 若有，任何新的非药典分析方法和验证数据详情

AN8) Deletion of a non significant in-process test applied during the manufacture of the final substance

Conditions:

- the change does not result from unexpected events arising during manufacture.

Specific Documentation:

- comparative table of approved and proposed in-process tests
- justification /risk-assessment from the certificate holder as appropriate showing that the parameter is non-significant.

AN8) 删除成品制造中不重要的中控检测和限度

条件

- 该变动原因不是生产过程的异常引起的

文件要求：

- 新旧中控检测对比表
- 证书持有者说明该参数不重要的证明/风险评估

AN9) Tightening of the limits of in-process tests applied during the manufacture of the final substance

Conditions:

- the change does not result from unexpected events arising during manufacture
- the test procedure remains the same, or changes in the test procedure are minor.

Specific Documentation:

- comparative table of approved and proposed in-process tests.

AN9) 提高成品制造中中控检测限度

条件

-该变动原因不是生产过程的异常引起的

-检测程序不变，或检测程序变化较小

文件要求：

-新旧中控检测对比表

AN10) Addition of a specification parameter for a starting material/intermediate/reagent

Conditions:

- the change does not result from unexpected events arising during manufacture
- any new test method does not concern a novel non-standard technique or a standard technique used in a novel way
- the test method is not a biological method or a method using a biological reagent for a biological substance (does not include standard pharmacopoeia microbiological methods).

Specific Documentation:

- comparative table of approved and proposed specifications
- details of any new analytical method and validation data, where relevant.

AN10)增加起始物料/中间体/试剂质量标准的参数

条件

- 该变动原因不是生产过程的异常引起的
- 任何新的检测方法不涉及新的非标准技术或以新方式使用的标准技术
- 检测方法不是生物方法或生物产品使用生物试剂的方法（不包括药典中标准的微生物方法）

文件要求：

- 新旧中控检测对比表
- 若有，任何新的分析方法和验证数据详情

AN11) Deletion of a non-significant specification parameter for the final substance/starting material/intermediate or deletion of a test procedure for a starting material/intermediate/ reagent

Condition:

- the change does not result from unexpected events arising during manufacture
- the parameter is non-significant or an alternative test procedure is already approved.

Specific Documentation:

- comparative table of approved and proposed specifications
- justification/ risk-assessment from the holder of the certificate as appropriate showing that the parameter is non-significant.

AN11) 删除成品/起始物料/中间体一个不重要的质量标准参数，或删除起始物料/中间体/试剂检测程序

条件：

-该变动原因不是生产过程的异常引起的

- 该参数不重要或一个可替代的检测程序已被批准

文件要求：

-新旧质量规格对比表
-证书持有者说明该参数不重要的证明/风险评估

AN12) Minor changes to a test procedure for a starting material/intermediate/reagent used in the manufacturing process of the final substance (former N7)
Conditions:
- the method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method)
- appropriate (re-)validation studies have been performed in accordance with relevant guidelines and show that the new updated test procedure is at least equivalent to the former one
- the final substance is not a biological substance.
Specific Documentation:
- updated method description.

AN12) 产品生产过程中所用到的起始物料/中间体/试剂分析方法的微小变更（以前的 N7）
条件:
- 分析方法本身不变(如：柱长或柱温改变，但柱子类别或方法不变);
- 已按有关指南要求进行适当的（再）验证，证明新检验方法至少等同于原方法
- 成品不是生物产品
文件要求
- 更新后的方法描述

AN13) Tightening of the specification limits for a starting material/ intermediate/reagent used in the manufacturing process of the final substance (former N8)
Conditions:
- the change should not be the result of unexpected events arising during manufacture
- any change should be within the range of currently approved limits
- the test procedure remains the same, or changes in the test procedure are minor.
Documentation
- comparative table of approved and proposed specifications

AN13)提高产品生产过程中所用到的起始物料/中间体/试剂质量标准（以前的 N8）
条件:
- 该变动不是生产过程的异常引起
- 所有变动必须符合现行已经批准的质量标准范围
- 检测方法不变或检测方法变化较小
文件要求
- 变动前后质量标准对照表

AN14) Change in the composition of the immediate packaging
Conditions:
- the proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties
- relevant stability studies have been started under ICH conditions and relevant stability

parameters have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal at time of implementation.
NB: if the proposed packaging is more resistant than the existing packaging, the three months stability data do not yet have to be available.
These studies must be finalized and the data will be provided immediately to EDQM if outside specifications or potentially outside specifications at the end of the re-test period (with proposed action).
- the final substance is not a sterile, liquid or biological substance.
Specific Documentation:
- comparison of the approved and proposed immediate packaging specifications, if applicable
- appropriate data on the new packaging including a confirmation that the material complies with relevant pharmacopoeial requirements or EU legislation on plastic materials and objects in contact with foodstuffs
- a declaration from the holder of the certificate as appropriate that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalized and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved re-test period (with proposed action).

AN14) 内包材成分变化
条件：
-在相关特性上，新旧包材至少等同
-按照 ICH 条件开始相应的稳定性实验，至少已有两批中试或正式生产批次进行了稳定性参数评估，执行时至少有符合质量标准的三个月的稳定性数据
NB: 若新包装比原包装更严格，三个月的稳定性数据不是必须的
如果复测期结束（按新包装）后不符合标准或可能不符合标准，须尽快完成这些研究并立即将数据提交给 EDQM。
- 产品不是无菌、液体或生物产品
文件要求：
- 若有的话，新旧内包装标准对比
-新包装的一些适当的数据，包括证明材料符合相关药典要求或欧盟对与食品接触的塑料材料与物体的法规
- 证书持有者申明：要求的稳定性实验已经按照 ICH 条件（指明批号）进行，执行时可提供符合要求的最少稳定性数据且数据没有问题。确定将完成实验，并且若在复测期（新标准）结束后出现不合格或可能不合格时会立即将数据上报给相关部门

AN15) Change in the specification parameters and/or limits of the immediate packaging of the final substance
Conditions:
- the change does not result from unexpected events arising during manufacture of the packaging material or during storage of the final substance
- the test procedure remains the same, or changes in the test procedure are minor

- any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Specific Documentation:

- comparative table of approved and proposed specifications.

AN15)成品内包材质量标准参数和/或限度改变

条件

- 变化不是由于包材生产或产品储存过程的异常产生的
- 检测方法不变或变化较小
- 任何新的检测方法不涉及新的非标准技术或以新方式使用的标准技术

文件要求

- 新旧标准对比表

NOTIFICATIONS FOR TSE CERTIFICATES (TIN/TAN)

1. Immediate notifications (TIN):

TIN1) Deletion of a source country or change in source of a material used in the preparation of the final substance from a TSE risk material to a vegetable, synthetic, or non-TSE risk material (former N12)

Conditions:

- no change in the manufacturing process.

Specific Documentation:

- if applicable a declaration from the certificate holder or manufacturer of the material that it is purely of vegetable, synthetic or non-TSE risk origin.

TSE 证书通知(TIN/TAN)

1. 立即通知 (TIN):

TIN1)取消该物质来源，或将产品制备中所使用的、具 TSE 风险的原料更改为植物的、合成的或无 TSE 风险的来源（以前的 N12）

条件： 生产工艺不得改变

文件要求： 适用时，证书拥有者或原料生产者声明原料仅仅来源于植物、合成或无 TSE 风险。

TIN2) Change or addition of a manufacturing site for the final substance when the proposed manufacturer is part of the same group as the approved manufacturer (former T1)

Conditions:

- no change in the manufacturing process, in the materials and in the origin of the material used in the process
- no other TSE risk material is processed in the new manufacturing site.

Documentation:

- a declaration from the holder of the certificate/manufacturer that the manufacturing process is identical to that already approved
- a declaration from the holder of the certificate/manufacturer that no other TSE risk material is processed in the new manufacturing site
- updated declarations of manufacture in accordance with the dossier and according to GMP

rules/quality system and of willingness to be inspected
- information on the quality assurance system (including traceability) applied in the new manufacturing site.

TIN2) 生产场地变动或增加，新厂家与原厂家同属一个集团（以前的 T1）
条件:
- 生产工艺不变，工艺过程中所使用物料及其来源不变
- 新厂址不生产其它具 TSE 风险的产品
文件要求
- CEP 证书持有人/生产厂声明：生产工艺与原来申报工艺完全相同
- CEP 证书持有人/生产厂声明：新厂址不生产其它具 TSE 风险的产品
- 更新以下声明：按申报文件组织生产、符合 GMP 和愿意接受检查
- 质量保证体系适用于新厂址的信息（包括可追踪性）

TIN3) Change in the quality assurance system applied in the manufacturing site (Former T3)
Conditions:
- the new quality assurance system is at least equivalent to the former one
- no change in the manufacturing process (including process parameters) or in the specifications of the final substance.
Documentation
- updated information on the quality assurance system (including traceability)
- updated declarations of manufacture in accordance with the dossier and according to GMP rules/quality system and of willingness to be inspected.

TIN3)生产场所质量保证体系变更（以前的 T3）
条件:
- 新质量体系至少与以前的体系具等同性
- 生产工艺（包括工艺参数）或产品质量标准不变
文件要求
- 更新的质量保证体系介绍（包括可追踪性）
- 更新以下声明：按申报文件组织生产、符合 GMP 法规/质量体系和愿意接受检查

2. Notifications with annual reporting (TAN):
TAN1) Minor change in the manufacturing process (including process parameters) or in the specifications of the final substance (Former T2)
Conditions:
- the change has no impact on the TSE risk
- the certificate of suitability covers only the TSE risk and does not cover the chemical purity and microbiological quality.
Documentation:
- comparison of the approved and proposed process
- a declaration from the holder of the certificate/manufacturer that the change has no impact on the TSE risk.
2. 每年报告的通知 (TAN):

TAN1) 生产工艺（包括工艺参数）或产品质量标准的微小变更（以前的 T2）
条件:
- 变更不影响 TSE 风险
- TSE 证书仅包括 TSE 风险，不涉及化学纯度及微生物质量
文件要求
- 变更前后的工艺对比
- 证书拥有者/生产者声明：变更不影响 TSE 风险

TYPICAL MINOR CHANGES FOR CERTIFICATES FOR CHEMICAL PURITY AND MICROBIOLOGICAL QUALITY
THIS IS A NON EXHAUSTIVE LIST OF MINOR CHANGES INTENDED TO HELP THE SUBMISSION AND THE PREPARATION OF THE DOCUMENTATION.
Change in batch size of the final substance or an intermediate more than 10-fold compared to the original batch size (former R2)
Specific Documentation:
- updated description of the full process specifying the new batch size
- batch analysis data (in comparative tabular format) on a minimum of one production batch manufactured according to both the approved and the proposed sizes.
化学微生物质量产品的典型微小变更
这是为了帮助提交和文件准备而列出的非全面的微小变更清单

成品或中间体批量放大超过原申报批量 10 倍（以前的 R2）
文件要求
- 变动后完整生产工艺描述，说明新的批量
- 批量变动前后至少一个批号的正式生产批分析数据(对比表格).

Change or addition of a manufacturer of a starting material or intermediate used in the manufacturing process of the final substance
Specific Documentation:
- a declaration from the holder of the Certificate of suitability that the synthetic route (or in case of herbal material, where appropriate the method of preparation, geographical source and production), the specifications and the quality control procedures of the starting material or intermediate are the same as those already approved
- a list of approved and proposed sites
- for a manufacturer of intermediate, declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected for the proposed site
- batch analysis data (in comparative tabular format) on a minimum of one production batch manufactured with the approved and the proposed sources of material.
变更或增加产品生产工艺中所使用的起始物料或中间体生产厂家
- CEP 证书持有者申明合成路线（或当产品为草药时，其制备方法，地理来源和制造）、起始物料或中间体的质量标准和检测方法与已批准的一致
- 新旧地址的清单
- 中间体生产厂家申明：按申报文件组织生产、符合 GMP 法规和愿意接受检查
- 使用新旧来源的物料正式生产的至少一个批次的产品批分析数据（对比表格）

Change or addition of a manufacturing site/workshop for the final substance

Specific Documentation:

- a declaration from the holder of the Certificate of suitability that the synthetic route (or in case of herbal material, where appropriate the method of preparation, geographical source and production), quality control procedures and specifications of the final substance are the same as those already approved
- a list of approved and proposed sites
- updated declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected for the proposed site
- batch analysis data (in comparative tabular format) on a minimum of one production batch manufactured in both the approved and the proposed sites.

变更或增加产品的生产地址/车间

文件要求：

- CEP 证书持有者申明产品的合成路线（或当产品为草药时，其制备方法，地理来源和制造）、产品的质量标准和检测方法与已批准的一致
- 新旧地址的清单
- 生产者更新声明：按申报文件组织生产、符合 GMP 法规或新地址愿意接受检查的声明
- 新旧地址至少一批正式生产批次的成品批分析数据（对比表格）

For a "double" Certificate of suitability (for chemical purity and microbiological quality and for TSE risk), change in source of a material used in the preparation of the final substance from a TSE risk material to a vegetable, synthetic, or non-TSE risk material (former R5)

Specific Documentation:

- updated specifications of the proposed source of the material
- batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the final substance from the approved and proposed source of the material or intermediate
- a declaration from the manufacturer of the material that it is purely of vegetable, synthetic or non-TSE risk origin (specifying the origin)
- a declaration from the holder of the certificate that there is no change in the manufacturing process and that the specifications of the final substance remain the same.

双重 CEP 证书（化学微生物和 TSE 证书），将产品制备中所使用的 TSE 风险原料改为植物、合成或非 TSE 风险原料来源（以前的 R5）

文件要求

- 新来源原料的质量标准
- 原料或中间体来源变更前后至少各两批产品（至少是中试批）批分析数据（对比表格）
- 原料生产厂声明：该原料仅仅来源于植物、合成或无 TSE 风险（说明来源）
- 证书持有者声明：产品生产工艺和质量标准不变

Extension/addition of the re-test period of the final substance and/or change in the storage conditions for the final substance (former R7)

Specific Documentation for addition of a re-test period:

- results of long-term and accelerated stability studies for at least two pilot or production scale batches

- appropriate data on the packaging material including a confirmation that the material complies with relevant pharmacopoeial requirements or EU legislation on plastic materials and objects in contact with foodstuffs.

Specific Documentation for an extension of the re-test period / change in the storage conditions for the final substance:

- updated results of stability studies for at least two pilot or production scale batches.

延长/增加产品复测期/改变产品贮存条件（以前的 R7）

增加复测期的文件要求：

- 提供至少两批中试或正式生产的长期和加速稳定性实验数据
- 关于包装材料的一些适当资料，包括证明材料符合相关药典要求或欧盟对与食品接触的塑料材料或物体的法规

延长复测期/改变产品贮存条件的文件要求：

- 更新至少两批中试或正式生产的稳定性实验数据

Change/addition of a manufacturer of starting material/intermediate used in the manufacturing process of a biological substance

Specific Documentation:

- a declaration from the holder of the certificate that the manufacturing process, quality control procedures and specifications of the final substance and of the concerned material are the same as those already approved
- a list of approved and proposed sites
- for a manufacturer of intermediate, declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected for the proposed manufacturer
- batch analysis data (in comparative tabular format) on 3 batches (minimum pilot scale) manufactured according to both the approved and the proposed manufacturers.

变更/增加生物产品生产工艺中所使用的起始物料/中间体生产厂家

文件要求

- CEP 证书持有者声明产品和相关原料的合成路线、检测方法和质量标准与已批准的一致
- 新旧地址的清单
- 中间体生产厂家声明：按申报文件组织生产、符合 GMP 法规和愿意接受检查
- 新旧地址各三批（至少中试批次）的产品批分析数据（对比表格）

Change/addition of the manufacturer of a biological substance

Specific Documentation:

- a declaration from the holder of the certificate that the manufacturing process, quality control procedures and specifications of the final substance are the same as those already approved
- batch analysis data (in a comparative tabular format) for at least 3 batches (minimum pilot scale) of the final substance from the approved and the proposed sites
- updated declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected.

变更/增加生物产品生产厂家

文件要求

- CEP 证书持有者申明产品的合成路线、检测方法和质量标准与已批准的一致
- 新旧地址各至少三批（至少中试批次）的产品批分析数据（对比表格）
- 更新声明：按申报文件和 GMP 法规组织生产和愿意接受检查

Minor changes in the manufacturing process of a biological substance, including change in batch size

Specific Documentation:

- a direct comparison of the approved and the proposed process
- a declaration from the holder of the certificate that the specifications of the final substance are the same as those already approved
- batch analysis data (in comparative tabular format) of at least 3 batches (minimum pilot scale) of the final substance manufactured according to the approved and proposed process or according to both approved and proposed batch sizes, demonstrating that the change has no negative impact on the quality of the final substance.

生物产品生产工艺微小变更，包括批量改变

文件要求

- 新旧工艺直接对比
- CEP 证书持有者申明产品的质量标准与已批准的一致
- 根据新旧工艺或新旧批量生产的各至少三批（至少中试批次）产品的批分析数据（对比表格），表明变更对产品质量无不良影响

Changes to a test procedure (including replacement or addition) for the biological substance/starting material/intermediate or changes to a biological method

Specific Documentation:

- description of the analytical method, a summary of validation data
- comparative analysis results showing that the approved and the proposed test are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

生物产品/起始物料/中间体检测方法变更（包括取代或增加）或变更为生物方法

文件要求：

- 描述分析方法，验证数据总结
- 对比数据表明新旧方法是等同的。该条不适用于增加新检测方法的情况

MAJOR CHANGES (MAJ)

MAJ1 – Change/addition of the manufacturer of a starting material or intermediate, when the proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which are likely to change the qualitative and/or quantitative impurity profile (eg. new reagents, solvents, materials are introduced in the synthesis)

MAJ2 - Change in the manufacturing process of the final substance that regards the sterilization step(s), including changes in batch size of a sterile substance

MAJ3 - Substantial change to the manufacturing process/addition of an alt-ernative manufacturing

process for a starting material, intermediate or final substance likely to change the qualitative and/or quantitative impurity profile (eg. new reagents, solvents, materials are introduced in the synthesis)

MAJ4 - Changes in the manufacturing process of a herbal substance related to geographical source or production

MAJ5 - Widening or deletion of approved in-process test limits, which may have a significant effect on the overall quality of the final substance

MAJ6 – Widening of the approved specifications limits for the final substance

MAJ7- Widening of the approved specifications limits for starting materials/ intermediates, which may have a significant effect on the overall quality of the final substance

MAJ8 - Deletion of a specification parameter which may have a significant effect on the overall

quality of the final substance

MAJ9 - Change in the composition of immediate packaging for a sterile substance

MAJ10 - Introduction of a new design space or extension of an approved design space or of a post approval change management protocol related to the final substance

重大变更 (MAJ)

MAJ1 –变更/增加起始物料或中间体的生产厂家，新厂家使用的合成工艺或生产条件与原厂家的有很大不同，可能会改变产品定性和/或定量的杂质情况（如在合成工艺中引入新试剂、新溶剂、新物料）

MAJ2 –产品灭菌步骤的生产工艺变更，包括无菌制品的批量变更

MAJ3 – 起始物料、中间体或产品的生产工艺变化较大/增加一个替代的生产工艺，可能会改变定性和/或定量的杂质情况（如在合成工艺中引入新试剂、新溶剂、新物料）

MAJ4 - 与地理产地或制造相关的草药的生产工艺变更

MAJ5 -放宽或删除中控限度，可能对产品总体质量产生重大影响

MAJ6 –放宽产品质量标准的限度

MAJ7-放宽起始物料/中间体的质量标准的限度，可能对产品总体质量产生重大影响

MAJ8 – 删除质量标准参数，可能对产品总体质量产生重大影响

MAJ9 - 无菌产品内包材成分改变

MAJ10 – 引入新的设计空间或放宽已批准设计空间，或引入与最终产品（API）相关的批准后的变更管理方案

TSE changes

MAJ11 – Change/addition of a source country or tissues for TSE risk material

MAJ12 - Change/addition of a manufacturer of a starting material or intermediate

MAJ13 – Change/addition of a manufacturing site where other TSE materials than the substance are processed

MAJ14 - Substantial changes in the manufacturing process that are likely to affect the TSE risk

TSE 变更

MAJ11 –变更/增加 TSE 风险物质的来源国或组织

MAJ12 -变更/增加起始物料或中间体生产厂家

MAJ13 –变更/增加生产厂地，（此生产厂地）也生产其他 TSE 风险物质

MAJ14 -可能会影响 TSE 风险的生产工艺重大变更

RENEWAL

The Certificate of suitability is valid for five years from the date when the original certificate was granted. Regardless of any revisions treated in the meantime, the holder of a Certificate of suitability shall ask for the renewal of the Certificate of suitability six months prior to expiry date by providing an update of the certification dossier.

If no change has been made since the last Certificate of suitability was granted

Documentation:

- a statement that no changes that may affect the quality, safety or efficacy of the final substance have been made
- certificates of analysis from at least two recent production batches
- updated declarations as appendixes to the application form.

更新

CEP 证书自首次签发之日起 5 年有效。失效前 6 个月，无论是否正在办理变更手续，CEP 证书持有人必须提出更新申请，并上报更新后的文件。

如果自上次 CEP 证书签发后没有任何变动

文件要求：

- 声明没有发生任何影响产品质量、安全、效力的变更
- 并提供至少两个最近批号的分析证明（COA）
- 刷新申请表格后附的声明

If changes are included in the request for renewal

Documentation:

- an updated dossier in CTD format and/or updated sections affected by the changes
- list of changes introduced in the format of a comparative table
- relevant data supporting each change as described in this guideline
- certificates of analysis from at least two recent production batches
- updated declarations as appendixes to the application form.

如果更新申请包含变更

文件要求：

- CTD 格式的更新文件/或受变更影响的更新部分
- 所做变更的比较表格
- 按本指南要求，提供每一个变更的支持性数据资料
- 提供至少两个最近生产批号的分析证明（COA）
- 刷新申请表格后附的声明

TRANSFER OF HOLDERSHIP OF A CERTIFICATE OF SUITABILITY

A transfer of the holdership of the Certificate of suitability (i.e. change in the name of the certificate holder that is not the same legal entity and where the change does not occur following a sale or a merger) is feasible in exceptional cases with the below conditions:

- the current Certificate of suitability is held by another company than the manufacturer
- the manufacturer takes out the Certificate of suitability in their own name.

Documentation:

- a letter signed by both parties, i.e. the former holder and the manufacturer, agreeing that the holdership of the Certificate of suitability is passed on to the manufacturer from the date of the request
- updated declarations as annex to the application form.

CEP 证书持有人转让

CEP 证书持有人的转让（即：证书持有人变更给原法人以外的团体，这种变更不是公司出售或合并的结果）在下面的条件下是可行的：

- 现行的 CEP 证书被另一个公司拥有，而不是该生产厂
- 生产厂以自己名义领取 CEP 证书

文件要求：

- 双方签字协议函，即：原持有人和生产厂同意自申请之日起，CEP 证书转让给生产厂持有。
- 刷新申请表格附件的声明