Technical guide for the ELABORATION OF MONOGRAPHS

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Technical Guide for the Elaboration of Monographs

欧洲药典质量标准的起草技术指南

——II.8~II.12 部分

II.8. ASSAY 含量测定

Assays are included in monographs unless:

除下列情况外，各论中应包括含量测定：

- all the foreseeable impurities can be detected and limited with sufficient accuracy and precision;
  所有可预见的杂质都能以足够的准确度和精密度被检测并将其含量限制在可接受的范围内；

- certain quantitative tests, similar to assays, are carried out with sufficient accuracy and precision (specific optical rotation, specific absorbance, etc.);
  已进行了与含量测定类似的某些定量检测，并有足够的准确度和精密度(比旋度、吸收系数等)；

- specific profiles of relevant substances such as composition of the fatty acid fraction (see general chapter 2.4.22. *Composition of fatty acids by gas chromatography*) or composition of the sterol fraction of a fat or fatty oil (see general chapter 2.4.23. Sterols in fatty oils) have been established;
  已确立了有关物质的具体概况，如脂肪酸的组分（见通则 2.4.22.气相色谱法测定脂肪酸的组分）或脂肪/脂肪油中甾醇的组分（见通则 2.4.23.脂肪油中的甾醇）已经确定；

- the tests performed are sufficient to establish the quality of the substance (typically for non-active substance, for example ethanol or water).
  所进行的检测足以确定该物质的质量（通常为非活性物质，例如乙醇或水）。

More than one assay may be necessary if:

如果出现下列情况，可能需要不止一种含量测定：

- the substance to be examined consists of a combination of two parts that are not necessarily present in absolutely fixed proportions, so that the assay of only one of the two constituents does not make it possible to determine the substance as a whole correctly (e.g. theophylline and ethylenediamine);
  要检查的供试品含有组成比例不固定的两部分物质，因此，只对两部分中的一部分进行含量检测不能正确地确定整个物质（例如茶碱和乙二胺）。

- the results of the quantitative tests do not fully represent the therapeutic activity, in which case a biological assay is included.
  定量检测的结果不能完全代表药物的治疗活性，在这种情况下，就需要进行生物学活性的测定。

In the case of well-defined salts, the assay of only one of the ions, preferably the pharmacologically active moiety, is generally considered sufficient. It is only rarely necessary to determine all the ions and, in any case, it is considered superfluous to determine one of these by 2 methods even when these depend on different principles.
对于定义明确的盐类，通常认为只检测其中一种具有药理活性的离子组分就足够了。很少有必要测定所有的离子，在任何情况下对任意一个离子采用两种方法进行测定都是不必要的，即使这两种方法的原理不同。

When the identification and purity tests are sufficiently specific and selective, a non-specific but precise assay may be used (e. g. by volumetric titration), rather than a specific and less precise assay. When an active substance is covered by a monograph and a monograph on the corresponding medicinal product already exists or is being elaborated, the same chromatographic assay procedure should ideally be described.
当鉴别和纯度测试具有足够的特异性和选择性时，可以使用非特异但精确的含量测定方法（例如，通过容量滴定法），而不是选择特异性强但不精确的含量测定方法。当一种活性物质被列入各论中，而相应的药品的各论已经存在或正在制定，最好是采用相同的色谱检测程序。

Every assay procedure proposed must be validated according to the procedures described for the different techniques in part III.

每个拟定的含量测定程序都必须按照本书第三部分中针对不同技术描述的程序进行验证。

II.8.1. Absorption spectrophotometry (utraviolet and visible) (2.2.25.)

吸收光光度法（紫外线和可见光）（2.2.25.）

UV-Vis spectrophotometric assays may be carried out directly or after a suitable chemical reaction. Other techniques are usually preferred. When monographs containing an assay based solely on UV-Vis spectrophotometry are revised, it is recommended to replace it with a chromatographic-separation-based assay or a titration.

UV-Vis 分光光度法含量可以直接进行检测，或在适当的化学反应后进行检测。其他方法通常是首选。当修改包含仅基于 UV-Vis 分光光度法含量的各论时，建议采用基于色谱分离的含量检测方法或滴定法取代它。

II.8.1.1 Direct measurement 直接测定法

This is not specific but may be of acceptable accuracy and precision and is usually performed without a reference substance: the absorbance of the solution is measured at the specified absorption maximum, and the content of the substance to be examined is calculated on the basis of the specific absorbance stated in the monograph.

本法不具有专属性，但可能具有可接受的准确性和精密度，测定中往往不需要对照品：在规定的最大吸收波长处测定供试品溶液的吸光度，并根据各论中给出的特定吸收系数计算待检物质的含量。

The specific absorbance value must be verified for a new substance. The manufacturer must supply validation data supporting the acceptance of the “true” value, otherwise this value needs to be validated by the (co-)rapporteur. These validation data include, for example, the purity of the substance used to determine the value, which is demonstrated by employing several methods (separation techniques, absolute methods, the response factors of likely impurities, solvents, etc.)

必须对新药的特定吸收值进行验证。制造商必须提供验证数据来支持“真实”值作为吸收值，否则该值需要由（共同）报告员进行联合验证。这些验证数据包括，如用于确定该值的物质的纯度，这可以通过采用几种方法（分离技术、绝对方法、杂质、溶剂等相关物质的响应因子）来证明。

With a reference substance, the active substance content is calculated by comparing the absorbance of the solution to be examined with that of a solution of the reference substance.
采用对照品法，通过比较待检溶液和对照品溶液的吸光度来计算活性物质的含量。

For experimental details and results, see general chapter *2.2.25. Ultraviolet and visible absorption spectrophotometry*.
实验细节和结果见总则 2.2.25“紫外-可见吸收分光光度法”。

II.8.1.2Measurement after a colour reaction 颜色反应后的测量
This measurement is carried out by comparison with a reference substance. The results may be less accurate and precise due to the sample treatment.
本法是通过与对照品的比较来进行的。由于样品处理的原因，结果可能不太准确和精密。

II.8.2. Volumetric analysis 容量分析

The amount of the substance taken for the assay is such that the final titration, using automatic titration equipment, will consume less than 10 mL – preferably 7 -8 mL – of titrant in order to permit the use of standard titration equipment. In the case of back-titration, the fixed volume of the first titrant added must also be adequate so that the result of the assay will not be based upon volumes that are too similar.
含量测定用供试品的量应满足如下条件：采用自动滴定仪时，最终滴定液的消耗体积不超过 10ml，最好是 7-8ml，这样可采用标准滴定仪进行容量分析。当采用返滴定法时，首先加入的滴定液的固定的体积必须适当，使得含量测定结果的计算不会基于过于相似的体积数。

Blank tests are to be prescribed whenever necessary, unless already stipulated in the corresponding general method. A blank test can be avoided when the composition of the medium in which a volumetric solution is standardised is the same as that in which it is to be used.
必要时应描述空白试验，除非在相应的通用方法中已有规定。当将要使用的介质的溶液成分与药典通用方法中所用介质的溶剂成分相同时，可以不进行空白试验。

Either potentiometric end-point detection or a visual colour change indicator can be specified

in the monograph, when an acid-base or redox titration is described. The potentiometric mode of end-point detection (*2.2.20. Potentiometric titration*) is clearly applicable in almost all cases.
各论中含量测定项下可以规定采用电位终点检测或视觉颜色变化指示剂法指示滴定终点，终点检测点位模式（2.2.20 电位滴定）几乎适用于所有情况。

Determination by visual colour change should be avoided except for complexometric titrations, where this is generally not possible. Where potentiometric detection is specified, the appropriate indicator electrode for that purpose is to be given in the text only if necessary (special type of electrode). The number of inflexion points to be evaluated is given. Other modes of detection may be specified, such as the amperometric method (*2.2.19. Amperometric titration*) or the voltametric method (*2.2.65. Voltametric titration*). Whichever mode is used, it must be known to be appropriately reproducible and preferably stoichiometrically exact. When a visual indicator is specified, the colour change is given only when it is different from that described in general chapter *4.1.1. Reagents*.
应避免通过视觉颜色变化进行测定，除非是复杂的滴定法。如果规定了电位检测，仅在必要时在文本中给出用于该目的的适当指示电极（特殊类型的电极）。应给出滴定反应的拐点数量。可指定其他检测模式，如安培法（2.2.19. 安培滴定法）或伏安法（2.2.65. 伏安滴定法）。无论采用哪种模式，都必须知道其具有适当的重现性，最好是精确的化学计量。当指定使用指示剂法时，只有当颜色变化与通则 4.1.1“试剂”中描述的不同时才会在正文中给出。

The following methods are recommended for the titration of halide salts of organic bases and some quaternary ammonium substances:
以下方法被推荐用于有机碱的卤化物盐以及某些季铵盐物质的滴定：

a) Alkalimetric titration in an alcoholic medium. This is the preferred option for the volumetric titration of halide salts. When carrying out the alkalimetric titration, it may be necessary to add 5 mL of 0.01 *M hydrochloric acid* before the titration and to measure the volume of titrant required between the two points of inflexion. However, it is advisable to test the feasibility of the titration before adding 0.01 M hydrochloric acid.
在酒精介质中进行碱滴定法。这是卤化物盐类容量滴定的首选方案。在进行碱滴定法时，可能需要在滴定前加入 5mL 0.01M 盐酸，并测量两个拐点之间所需的滴定液体积。然而，在加入 0.01M 盐酸之前，最好先测试一下滴定的可行性。

b) Titration with perchloric acid, the sample being dissolved in anhydrous acetic acid before adding acetic anhydride or a mixture of acetic anhydride and anhydrous formic acid.
用高氯酸进行滴定，在加入乙酸酐或乙酸酐与无水甲酸的混合物之前，将样品溶解在无水乙酸中。

c) Argentimetry.
银量法。

d) Methods a) (with the addition of 5 mL of 0.01 *M hydrochloric acid*), and b) are often suitable for quaternary ammonium substances.
方法 a)（加入 5mL 0.01M 盐酸）和方法 b)通常适用于季铵盐的滴定。

II.8.3. Chromatography-based techniques 基于色谱法的技术

In pharmacopoeial practice , the chromatographic techniques on which assays may be based are normally limited to LC and GC. The recommendations contained in part II.7.8 on related substances for LC and GC will also be valid for developing assays based on these techniques. The use of an external standard in LC and the addition of an internal standard in GC are recommended. Such methods require the use of a CRS with an assigned content (see part I.7. Reference Standards)
在药典实践中，含量测定所依据的色谱技术通常仅限于 LC 和 GC。在 II.7.8 部分有关物质项下 LC 和 GC 的建议也将适用于开发基于这些技术的检测方法。建议 LC 使用外标法，GC 使用内标法。此类方法需要使用具有指定含量的 CRS（见第 I.7 部分：标准物质）。

II.8.4. Determination of nitrogen by sulfuric acid digestion (2.5.9.)

经硫酸消解的氮测定法(2.5.9.)

Any substance to be assayed by this method has a digestion time assigned after a determination of its digestion profile.
任何采用本法进行含量测定的药物，在测定其消解产物后，都要确定一个消化的时间。

The digestion profile may be determined as follows. Several individually weighed portions of

the prescribed amount of substance are assayed in accordance with the general method whilst varying the time for which the reaction mixture is boiled, normally up to 120 min, after the mixture has cleared. By plotting the resulting nitrogen content against the boiling time, it is possible to determine the minimum digestion time necessary to obtain constant values. In cases where the necessary digestion time exceeds 30 min, the time required is indicated in the monograph.

可按照下述方法测定其消解产物。按照附录项下的规定，称量几份规定数量的供试品及试剂。改变从反应混合物变清亮后，继续加热至沸腾并保持沸腾状态的时间，一般最长为 120 分钟。通过绘制氮含量测定结果与沸腾时间作的关系曲线，可以确定消解所需的最短时间。当需要的消解时间超过 30 分钟时，正文中应给出消解的时间。

II.9. STORAGE 储存

Although the statements given under this heading in a monograph of the Ph. Eur. do not constitute pharmacopoeial requirements, the appropriate information to safeguard the quality of a pharmacopoeial material during storage is to be given here where appropriate.

尽管在药典各论中，本标题项下的说明并不构成药典要求，为保证药典收载的物质在储存期间的质量，适当情况下，可在此项下给出适当的信息。

The terminology given in the General Notices and in general chapter 3.2. Containers should be used. Protection against loss or uptake of constituents via the gas phase requires an “airtight container”. A “sealed container” is also “tamper-evident”, while the converse is not necessarily true.

储存项下的术语参见凡例和通则 3.2“容器”。值得注意的是“密闭容器”并不意味着该包装可以防止气态物质的交换（溢出或吸收），要达到这一目的需要采用“密封的容器”。一个“严封的容器”同时也是具有防破坏功能的“安全包装”，反过来讲，安全的包装并不意味着一定是严封的包装。

Manufacturers should be requested to provide stability data. In considering the guidance to be given in the monograph, the behaviour of the material towards exposure to atmospheric air, various degrees of humidity, different temperatures and actinic light are to be taken into account. Where a substance is described in the CHARACTERS section as hygroscopic, deliquescent or sensitive to air, “airtight container” is indicated. When a substance is known to

be sensitive to actinic light, “protected from light” is indicated.
应要求药品生产企业提供稳定性数据。考虑到各论中需要给出的指导意见，应考虑到物料暴露于空气、不同湿度、不同温度和日光下等条件的稳定性情况。如果物质在特性部分中被描述为吸湿性、潮解性或对空气敏感，则应注明“密闭容器”。如果已知某种物质对光照敏感，则应注明“避光”。

In this context, it must be borne in mind that the method given in general chapter 5.11. Characters section in monographs for hygroscopicity is not to be used to define storage conditions. This is a rapid method that gives an indication of the hygroscopicity of the substance as an aid to the analyst so that the proper handling precautions can be taken when examining the substance in laboratory conditions.
在这种情况下，必须牢记，各论中通则 5.11 特性中给出的吸湿性方法并不适用于储存条件的定义。只是给出了指示物质引湿性的一个快速的方法，以作为分析人员的辅助手段，可在实验室条件下检查物质吸湿性时采取适当的处理措施。

II.10. LABELLING 标签

Since the labelling of medicine is subject to international agreements and supranational and national regulations, the indications given under LABELLING are not exhaustive: they consist of both mandatory statements (necessary for the application of the monograph) and other statements that are included only as recommendations. In general, for bulk active substances, the requirements given in this section of a pharmacopoeial monograph are confined to those essential for the correct interpretation of the other requirements in the monograph.
考虑到药品的标签需要服从国际协议、区域性（国家间联盟）以及国家的监管，因此，《欧洲药典》正文标签项下的信息并不详尽。标签的内容包含了强制性内容（申请《欧洲药典》收载的必须内容）以及其他的仅作为建议的内容。总之，对于原料药（活性成分），药典正文中标签项下的内容仅限于向用户正确地解释各论中的其他检测项目及要求。

When, for example, a starting material has to comply with additional requirements (e.g. sterility), the label must state, where appropriate, that the contents of the container are suitable for that use. Furthermore, when the inclusion of certain stabilisers or other additives is authorised by the monograph, their presence will generally have to be declared on the label.

例如，当一种起始物料必须符合额外的要求（如无菌性）时，该物料的标签项下必须注明该要求，说明容器内物质适用于该用途。另外，如果各论允许添加某些稳定剂或者其他添加物时，必须在标签中注明相关信息。

II.11. IMPURITIES 杂质

Monographs on organic chemicals should have an IMPURITIES section defining the impurities that are known to be detected by the prescribed tests and that have been considered in defining the acceptance criteria for related substances. Subheadings are given for “Specified impurities” and “Other detectable impurities” .All specified impurities covered by the monograph are included in this section. In addition, it may be useful to include information on other detectable impurities, (impurities whose detection by the monograph tests is known and has been experimentally verified but that are not known to occur in current production batches above the identification threshold).

有机化学品的正文项下应有“杂质”部分。也就是按照规定的方法需要进行杂质控制，并在有关物质中对其限度进行规定。药典中的杂质分为“特定杂质”和“其他可检测的杂质”，各论所涉及的所有特定杂质都包括在杂质项下。另外，提供其他可检测的杂质（正文检查项下需要检查的杂质，其含量超过鉴定限度，但属于当前生产批次产品中的未知杂质）的信息也有帮助作用。

The IMPURITIES section gives a list showing the chemical structure and chemical nomenclature (of the base/acid/neutral substance, not as the salt) for each impurity. Impurities are designated by a capital letter (A, B, C, D, etc.). Trivial names may be included in parenthesis in cases where they are considered to be informative.

杂质项下给出了每个杂质的化学结构和化学命名（酸或碱的形式，而不是盐），杂质用大写字母表示（A,B,C,D 等）。当认为杂质的别名有助于理解时，则可以列入在括号中。

The IMPURITIES section may also give information on the tests that limit a given impurity, for example where this test is not a “Related substances” test (e.g. enantiomeric purity) or where there is more than one “Related substances” test.

杂质项下也可能会给出需要控制的给定杂质的信息，比如，当这个杂质不是“有关物质”检查项下控制的杂质（如对映体纯度）或者有多个“有关物质”检查方法的情况。

II.12. FUNCTIONALITY-RELATED CHARACTERISTICS 功能性指标

Monographs on excipients may have a section on FUNCTIONALITY-RELATED CHARACTERISTICS (FRCs).

辅料的各论可能有一个“功能性指标”（FRCs）的章节。

This is introduced by a standard paragraph indicating the non-mandatory status. The uses for which each FRC is relevant are also stated. FRCs may be presented by:

这是一种由标准段落引入的，属于非强制执行的内容。同时还说明了每个 FRCs 的相关作用。FRCs 可能会以下列方式呈现：

- giving simply the name;
  仅仅给出名称；
- giving the name and a recommended method from the general chapters of the Ph. Eur.;
  给出《欧洲药典》通则项下的名称或者推荐的方法；
- giving the name, a recommended method and typical values;
  给出名称、推荐的方法和典型值；
- giving the name and a cross-reference to a test present in the mandatory part of the monograph.
  给出名称以及与各论中强制性测试部分的对照索引。