In Vitro Companion Diagnostic Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on: August 6, 2014

The draft of this document was issued on July 14, 2011.

For questions regarding this document that relate to CDRH contact Elizabeth Mansfield, at 301-796-4664, or elizabeth.mansfield@fda.hhs.gov; for questions for CBER contact Office of Communication, Outreach and Development (OCOD) at 240-402-7800 or 1-800-835-4709, or ocod@fda.hhs.gov. For questions for CDER, contact Christopher Leptak at 301-796-0017, or christopher.leptak@fda.hhs.gov.

U.S. Department of Health and Human Services Food and Drug Administration Center for Devices and Radiological Health
Center for Biologics Evaluation and Research Center for Drug Evaluation and Research

Preface

Public Comment

You may submit written comments and suggestions at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, (HFA-305), Rockville, MD, 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number FDA-2011-D-0215. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number (*1737)* to identify the guidance you are requesting.

Additional copies of this guidance document are also available from:

Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Room 3128, Silver Spring, MD 20993- 0002, or by calling 1-800-835-4709 or 240-402-7800, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

or

Center for Drug Evaluation and Research Division of Drug Information
10903 New Hampshire Ave., Bldg. 51, rm. 2201 Silver Spring, MD
20993-0002 Tel: 301-796-3400; Fax: 301-847-8714; E-mail:
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Table of Contents

Guidance for Industry and Food and Drug Administration Staff

In Vitro Companion Diagnostic Devices

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

This guidance is intended to assist (1) sponsors who are planning to develop a therapeutic product[1] (either a novel product or an existing product with a new indication) for which the use of an in vitro companion diagnostic device (or test) is essential for the therapeutic product's safe and effective use and (2) sponsors planning to develop an in vitro companion diagnostic device that is intended to be used with a corresponding therapeutic product.

Specifically, the guidance intends to accomplish the following:

- Define *in vitro companion diagnostic device* (hereafter referred to as an "IVD companion diagnostic device")
- Explain the need for FDA oversight of IVD companion diagnostic devices
- Clarify that, in most circumstances, an IVD companion diagnostic device and its corresponding therapeutic product should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product labeling

[1] As used in this guidance, *therapeutic product* includes therapeutic, preventive, and prophylactic drugs and biological products. Although this guidance does not expressly address therapeutic devices intended for use with in vitro diagnostics, the principles discussed in this guidance may also be relevant to premarket review of such devices.

- Provide guidance for industry and FDA staff on possible premarket regulatory pathways and FDA's regulatory enforcement policy
- Describe certain statutory and regulatory approval requirements relevant to therapeutic product labeling that stipulates concomitant use of an IVD companion diagnostic device when use of the IVD is essential to the safe and effective use of the therapeutic product

FDA encourages sponsors considering developing either the therapeutic product or IVD companion diagnostic devices discussed in this guidance to request a meeting with both relevant device and therapeutic product review divisions to ensure that the product development plan(s) will produce sufficient data to establish the safety and effectiveness of both the IVD companion diagnostic device and the therapeutic product.

This guidance document does not address the tests performed to establish the matching of a donor's blood, blood components, cells, tissue, or organs with that of a potential recipient, which are dealt with in the broader regulatory scheme of FDA's regulation of blood and human cells, tissues, and tissue-based products. Although Human Leukocyte Antigen (HLA) assays are often used to establish the matching of a donor and a potential recipient, they may have other uses as well. When used for such other purposes, HLA assays that are essential for the safe and effective use of a therapeutic product would fall within the scope of this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

II. Background

Diagnostic tests have been used for many years to enhance the use of therapeutic products. Tests are also used during therapeutic product development to obtain the data FDA uses to make regulatory determinations. After a therapeutic product is commercially available for use, health care professionals may use a relevant diagnostic test, for example, to select the appropriate therapy for a particular patient or to optimize a dosing regimen.

Recently, the development of therapeutic products for which the use of a diagnostic test is essential for the products to meet their labeled safety and effectiveness claims has become more common. For example, such a test can identify appropriate subpopulations for treatment or identify populations who should not receive a particular treatment because of an increased risk of a serious side effect. These new technologies are making it increasingly possible to individualize, or *personalize,* medical therapy by identifying patients who are most likely to respond, or who are at varying degrees of risk for a particular side effect.

When an appropriate scientific rationale supports such an approach, FDA encourages the joint development of therapeutic products and diagnostic devices that are essential for the safe and effective use of those therapeutic products. Several examples of such approved therapeutic/diagnostic pairs exist.[2]

When results from a diagnostic device are essential in patient treatment, health care professionals must be able to rely on those results. Inadequate performance of an IVD companion diagnostic device could have severe therapeutic consequences. Such a device might fail analytically (e.g., by not accurately measuring the expression level of a protein of interest), or clinically (e.g., by not identifying those patients at increased risk for a serious adverse effect). Erroneous IVD companion diagnostic device results could lead to withholding appropriate therapy or to administering inappropriate therapy. Therefore, FDA believes that use of an IVD companion diagnostic device with a therapeutic product raises important concerns about the safety and effectiveness of both the IVD companion diagnostic device and the therapeutic product. Because an IVD companion diagnostic device with inadequate "performance characteristics"[3] or other issues related to safety and effectiveness could expose a patient to avoidable treatment risks,[4] FDA will assess, through premarket review and clearance or approval, the safety and effectiveness of the IVD companion diagnostic device as used with the therapeutic product.

To facilitate the development and approval of therapeutic products that are intended for use with IVD companion diagnostic devices, as well as the development of the IVD companion diagnostic devices themselves, FDA is clarifying relevant policies related to these devices and products. FDA is also developing appropriate internal policies and procedures to ensure effective communication among the relevant centers and to promote consistent advice, efficient development of IVD companion diagnostic devices and therapeutic products, and coordinated product reviews for these devices and therapeutic products.[5]

[2] One example of a currently approved IVD companion diagnostic device that illustrates the importance of established performance parameters for both the therapeutic product and the IVD companion diagnostic device is FDA approved HER-2 tests to determine whether a patient may be a candidate for Herceptin (trastuzumab) therapy, which is indicated for treatment of metastatic breast cancer and gastric cancer. Herceptin lacks effectiveness in the HER-2 marker negative population, and also has the possibility of causing severe adverse effects. Therefore it is important to use an IVD companion diagnostic device to identify only those patients who could benefit from the therapy. [3] See 21 CFR 809.10 (b)(12). [4] Avoidable treatment risks may include adverse reactions, or failure to realize benefit from a different drug. [5] FDA expects that most therapeutic product and IVD companion diagnostic device pairs will not meet the definition of "combination product" under 21 CFR 3.2(e). It is not necessary to contact the Office of Combination Products about whether a therapeutic product and IVD companion diagnostic device pair is a combination product unless recommended by CDER, CBER, or CDRH. FDA intends to require separate marketing applications for a therapeutic product and an IVD companion diagnostic device intended for use with that therapeutic product regardless of whether the products could constitute a combination product. See 21 CFR 3.4(c). The standards for review, approval or clearance would be the same whether or not the therapeutic product and the IVD companion diagnostic device pair were considered a combination product. For information on investigational applications for these products, see Section VI.

III. Definition and Use of an IVD Companion Diagnostic Device

An *IVD companion diagnostic device* is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, including the labeling of any generic equivalents of the therapeutic product.

An IVD companion diagnostic device could be essential[6] for the safe and effective use of a corresponding therapeutic product to:

- Identify patients who are most likely to benefit from the therapeutic product
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product
- Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness
- Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population

FDA does not include in this definition in vitro diagnostic tests that are not essential to the safe and effective use of a therapeutic product.[7]

Ideally, a therapeutic product and its corresponding IVD companion diagnostic device should be developed contemporaneously, with the clinical performance and clinical significance of the IVD companion diagnostic device established using data from the clinical development program of the corresponding therapeutic product. However, FDA recognizes there may be cases when contemporaneous development may not be possible. An IVD companion diagnostic device may be a novel IVD device (i.e., a new test for a new analyte), a new version of an existing device developed by a different manufacturer, or an existing device that has already been approved or cleared for another purpose.

[6] When use of a diagnostic device is required in the labeling of a therapeutic product, e.g., for selection of appropriate patients for therapy, or to select patients who should not use the product, or for monitoring patients to achieve safety or effectiveness, use of the diagnostic device is considered "essential" for the purposes of this guidance. Uses of diagnostic devices that are suggested but not required in therapeutic product labeling are not considered "essential."

[7] Examples of such clinical laboratory tests are commonly used and well understood biochemical assays (e.g., serum creatinine or transaminases) that are used to monitor organ function, but are not essential for the safe and effective use of a therapeutic product.

The following section outlines FDA's policy regarding approval of a therapeutic product for use with a corresponding IVD companion diagnostic device.

IV. Review and Approval of IVD Companion Diagnostic Devices and Therapeutic Products

Applications for an IVD companion diagnostic device and its corresponding therapeutic product will be reviewed and approved according to applicable regulatory requirements. The IVD companion diagnostic device application will be reviewed and approved or cleared under the device authorities of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and relevant medical device regulations; the therapeutic product application will be reviewed and approved under section 505 of the FD&C Act (i.e., drug products) or section 351 of the Public Health Service Act (i.e., biological products) and relevant drug and biological product regulations. FDA intends to review each IVD companion diagnostic device submission within the context of, or in conjunction with, its corresponding therapeutic product, and FDA review of the IVD companion diagnostic device and the therapeutic product will be carried out collaboratively among relevant FDA offices.

A. Novel Therapeutic Products

For a novel therapeutic product for which an IVD companion diagnostic device is essential for the safe and effective use of the product, the IVD companion diagnostic device should be developed and approved or cleared contemporaneously so that it will be available for use when the therapeutic product is approved. Before approving the therapeutic product, FDA will determine that the IVD companion diagnostic device is properly validated and meets the applicable standard for safety and effectiveness or for substantial equivalence for the use indicated in the therapeutic product's labeling. The use of the IVD companion diagnostic device will be stipulated in the labeling of the therapeutic product (i.e., the therapeutic product is considered safe and effective *only* if used with the IVD companion diagnostic device). If FDA determines that an IVD companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, FDA generally will not approve the therapeutic product or new therapeutic product indication if the IVD companion diagnostic device is not approved or cleared for that indication. Approval or clearance of the IVD companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population.

B. Approval of a Therapeutic Product without an Approved or Cleared IVD Companion Diagnostic Device

FDA may decide that it is appropriate to approve a therapeutic product even though an IVD companion diagnostic device is not approved or cleared contemporaneously. Two such scenarios are discussed in this section. In general, if a therapeutic product is approved without approval or clearance of an IVD companion diagnostic device, FDA expects that an IVD companion diagnostic device that is intended for use with the therapeutic product will be subsequently approved or cleared through an appropriate device submission, and the therapeutic product labeling will be revised to stipulate the use of the IVD companion diagnostic device. In addition, FDA will consider whether additional protections are necessary to address the safety issues presented by the use of the therapeutic product without an approved or cleared IVD companion diagnostic device.[8]

1. New Therapeutic Products to Treat Serious or Life-Threatening Conditions

FDA may decide to approve a therapeutic product even if an IVD companion diagnostic device is not yet approved or cleared when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device. This will be determined by FDA during product review.

2. Already Approved Therapeutic Products

FDA will generally not approve a supplement to an approved therapeutic product application to update that product's labeling until the IVD companion diagnostic device is approved or cleared. Nevertheless, FDA recognizes that there may be occasions when the labeling for an already approved therapeutic product must be revised to address a serious safety issue. Under these circumstances, if the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device, FDA does not intend to delay approval of changes to the labeling of the therapeutic product until the IVD companion diagnostic device is approved or cleared.

C. General Policies

If the use of an IVD companion diagnostic device is essential for the safe and effective use of a therapeutic product, an approved or cleared IVD companion diagnostic device should be available for use once the therapeutic product is approved. FDA expects that the therapeutic product sponsor will address the need for an approved or cleared IVD companion diagnostic device in its therapeutic product development plan. The sponsor of the therapeutic product can decide to develop its own IVD companion diagnostic device; the sponsor can partner with a diagnostic device sponsor to develop the appropriate IVD companion diagnostic device; or the sponsor can explore modification of an existing IVD diagnostic device (its own or another sponsor's with that sponsor's agreement) to accommodate the appropriate device intended use. The following general policies apply whether a therapeutic product and its IVD companion diagnostic device are developed and manufactured by the same, or different, entities:

[8] Safety measures might include a risk evaluation and mitigation strategy (REMS), or a postmarket requirement, if necessary.

- FDA will apply a risk-based approach to determine the regulatory pathway for IVD companion diagnostic devices, as it does with all medical devices. This means that the regulatory pathway will depend on the level of risk to patients, based on the intended use[9] of the IVD companion diagnostic device and the controls necessary to provide a reasonable assurance of safety and effectiveness. Thus, the level of risk together with available controls to mitigate risk will establish whether an IVD companion diagnostic device requires a premarket approval application (PMA) or a premarket notification submission (510(k)).[10] FDA recommends that sponsors consult early with FDA on the likely regulatory pathway for the IVD companion diagnostic device. Premarket review by FDA will determine whether the IVD companion diagnostic device has adequate performance characteristics for its intended use.
- After completing review of the applications for a therapeutic product and an IVD companion diagnostic device and after determining that both products are ready for approval or approval and clearance, FDA intends to issue approvals or approval and clearance for both products at the same time (unless the Agency determines that approval of the drug prior to approval or clearance of the device is appropriate, as described in Section IV. B, above). FDA strongly encourages sponsors to time their clinical developments and premarket submissions to facilitate concurrent review.
- If an IVD diagnostic device is already legally marketed and the IVD diagnostic device manufacturer intends to market its device for a new use as an IVD companion diagnostic device for a novel therapeutic product, FDA would likely consider the new use of the IVD diagnostic device with the novel therapeutic product as a new use for the device that would require an additional premarket submission (see 21 CFR 807.81(a)(3)(ii), 814.39(a)).
- New IVD companion diagnostic devices intended to be used in the same manner as an existing approved or cleared IVD companion diagnostic device (e.g., different manufacturer, different technological characteristics) will be reviewed under a PMA or a traditional 510(k), as appropriate.

V. Labeling

A. Therapeutic Product Labeling

The FD&C Act requires the labeling of prescription therapeutic and device products to include the information health care professionals need to use the products (21 U.S.C. 352(f), 21 CFR 201.100(c)(1), 801.109(c) and (d)). The labeling often includes information about diagnostic tests that determine how, when, or whether a therapeutic product is used. The regulations for drug and biological product labeling expressly recognize the importance of diagnostic tests for the safe and effective use of these therapeutic products. According to the

[9] As used here, "indications" is considered a part of "intended use."[10] Experience indicates that most IVD companion diagnostic devices will be Class III devices, although there may be cases when a Class II classification with premarket notification (510(k)) is appropriate.

labeling regulations for drugs and biological products (21 CFR 201.56 and 57), product labeling must include information about (1) specific tests necessary for selection or monitoring of patients who need a drug; (2) dosage modifications in special patient populations (e.g., in groups defined by genetic characteristics); and (3) the identity of any laboratory test(s) helpful in following a patient's response or in identifying possible adverse reactions. The labeling regulations identify labeling sections where such discussion is appropriate (e.g., Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, Use in Specific Populations). For example:

- If a drug or biological product has been shown to be safe and effective in only a certain patient population identified by a diagnostic test, the Indications and Usage section must clearly define the patient population in whom the drug is approved (21 CFR 201.57(c)(2)(i)(B) and (C)).
- If a diagnostic test is essential for monitoring either therapeutic or toxic effects, the type of test must be identified under Warnings and Precautions (21 CFR 201.57(c)(6)(iii)).

Because it is important that the approved labeling for an IVD companion diagnostic device and its corresponding therapeutic product be complete and consistent, FDA makes the following clarifications:

- Ordinarily, information about the use of an IVD companion diagnostic device will be included in the labeling of its corresponding therapeutic product when the device meets the definition of an IVD companion diagnostic device (see Section III).
- The therapeutic product labeling should specify use of an FDA approved or cleared IVD companion diagnostic device, rather than a particular manufacturer's IVD companion diagnostic device. This will facilitate the development and use of more than one approved or cleared IVD companion diagnostic device of the type described in the labeling for the therapeutic product.
- In cases when an IVD companion diagnostic device is approved or cleared and is marketed *after* the therapeutic product is approved, the therapeutic product labeling should be updated to refer to the use of this type of IVD companion diagnostic device (21 CFR 201.56(a)(2)).

B. IVD Companion Diagnostic Device Labeling

The labeling for an in vitro diagnostic device is required to specify the intended use of the diagnostic device (21 CFR 809.10(a)(2)). Therefore, an IVD companion diagnostic device that is intended for use with a therapeutic product must specify the therapeutic product(s) for which it has been approved or cleared for use. In some cases, if evidence is sufficient to conclude that the IVD companion diagnostic device is appropriate for use with a class of therapeutic products, the intended use/indications for use should name the therapeutic class, rather than each specific product within the class.

When an IVD companion diagnostic device has been approved or cleared for use with a therapeutic product in one disease or setting, a PMA supplement or new 510(k), as appropriate, will be needed to expand the IVD companion diagnostic device labeling to include additional IVD companion diagnostic device indications, e.g., use of the same therapeutic that is now approved for use in a different disease or setting.

When an IVD companion diagnostic device has been approved or cleared for use with one therapeutic product and evidence becomes available that use of the same device is essential for the safe and effective use of a different therapeutic product, the IVD companion diagnostic device labeling should be expanded through approval or clearance of a new premarket submission (PMA or 510(k) as appropriate) or PMA supplement (see Section IV, above) to include the new therapeutic product. Labeling of the therapeutic product should also be amended through submission of a supplement.

VI. Investigational Use

IVD companion diagnostic devices used to make treatment decisions in clinical trials of a therapeutic product generally will be considered investigational devices, unless employed for an intended use for which the device is already approved or cleared. If used to make critical treatment decisions, such as patient selection, treatment assignment, or treatment arm, a diagnostic device generally will be considered a significant risk device under 21 CFR 812.3(m)(3) because it presents a potential for serious risk to the health, safety, or welfare of the subject, and the sponsor of the diagnostic device will be required to comply with the investigational device exemption (IDE) regulations that address significant risk devices.

If a diagnostic device and a therapeutic product are to be studied together to support their respective approvals (or clearance as appropriate for the diagnostic device), both products can be studied in the same investigational study, if the study is conducted in a manner that meets both the requirements of the IDE regulations (21 CFR Part 812) and the investigational new drug (IND) regulations (21 CFR Part 312). Depending on details of the study plan and participants, a sponsor may seek to submit an IND alone, or both an IND and an IDE. Sponsors should consult with the therapeutic product center and the relevant device center as to which approach is best or necessary for a particular study.

Information about the planned use of an IVD companion diagnostic device and its use in clinical trials should be included in an investigational submission. This information will help FDA understand and provide advice on how the IVD device will be used to enroll subjects into the trial(s) and how the test will be validated for use. For therapeutic product INDs that contain information about the investigational device, the therapeutic product review center (Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research) will engage appropriate expertise from the diagnostic product review center (Center for Devices and Radiological Health or Center for Biologics Evaluation and Research), and joint advice will be provided to the sponsor.

In addition, it will be helpful if both the IVD companion diagnostic device sponsor and the therapeutic product sponsor participate in discussions about the proposed IVD companion diagnostic device and solicit FDA feedback via the pre-submission process (a consultative submission through which device sponsors may obtain information that may help guide product development, e.g., information concerning appropriate validation studies) with the diagnostic review center. This will enable a more focused and in-depth discussion about the validation of the IVD companion diagnostic device and will aid in planning for a device PMA or 510(k) that is complete and timely. When appropriate, expertise from the relevant therapeutic product review center will be included in the diagnostic review center meetings.

FDA strongly encourages sponsors considering developing the products discussed in this guidance to request a meeting with both relevant device and therapeutic product review divisions as early in development as possible.

薬食審査発0701第10号平成２５年
７月１日

各都道府県衛生主管部（局）長殿

厚生労働省医薬食品局審査管理課長
（　公　印　省　略　）

コンパニオン診断薬等及び関連する医薬品の承認申請に係る留意事項について

昨今の科学技術の進歩に伴い、患者の遺伝子やタンパク質などを調べ、患者に応じた治療方法を選択する個別化医療が進展しており、特定の標的分子の発現等を前提とした分子標的薬等の開発等に伴い、治療に際して治療薬の選択等に用いられる診断薬等の重要性が認識されるようになっている。

これらの個別化医療に係る医薬品と対応する診断薬のより適切な開発を推進する観点から、今般、治療薬の選択等に用いられることにより個別化医療に資する診断薬等（以下「コンパニオン診断薬等」という。）及び関連する医薬品の取扱いについて、下記のとおりとすることとしたので、御了知の上、貴管下関係業者に対し指導方ご配慮願いたい。

なお、個別の事案に関わる具体的内容については、必要に応じ、独立行政法人医薬品医療機器総合機構（以下「PMDA」という。）との相談が推奨される点についてもあわせて周知願いたい。

記

１コンパニオン診断薬等の範囲

コンパニオン診断薬等とは、特定の医薬品の有効性又は安全性の向上等の目的で使用する次のいずれかに該当するものであって、当該医薬品の使用に不可欠な体外診断用医薬品又は医療機器（単に疾病の診断等を目的とする体外診断用医薬品又は医療機器を除く。）であること。

（１）特定の医薬品の効果がより期待される患者を特定するための体外診断用医薬品又は医療機器

（２）特定の医薬品による特定の副作用について、それが発現するおそれの高い患者を特定するための体外診断用医薬品又は医療機器

（３）特定の医薬品の用法・用量の最適化又は投与中止の判断を適切に実施するために必要な体外診断用医薬品又は医療機器

２コンパニオン診断薬等及び関連する医薬品の承認申請及び治験の届出に係る取扱い

（１）承認申請に係る留意事項

アコンパニオン診断薬等を用いる必要がある医薬品であって、当該コンパニオン診断薬等が承認されていない場合には、原則として、当該医薬品の承認申請を行う際は、同時期に当該コンパニオン診断薬等の承認申請が行われるべきであること。そのために、当該医薬品の申請者は、コンパニオン診断薬等の開発について、自ら、又はあらかじめコンパニオン診断薬等に係る他の開発企業と連携し、双方で開発や申請に必要な情報の共有に努めるなどして、十分に推進すべきであること。

イ上記アに関し、コンパニオン診断薬等及び関連する医薬品について、両者を同時期に承認申請する場合は、承認申請書の備考欄に、その旨をそれぞれ記載すること。

（２）治験の届出に係る留意事項

ア医薬品の治験の届出にあたり、対応するコンパニオン診断薬等の開発が行われている場合には、治験届の備考欄にその旨を記載すること。また、当該コンパニオン診断薬等の開発状況について、可能な範囲で簡潔に記載すること。治験依頼者とは別の企業が当該コンパニオン診断薬等を輸入し、当該企業が品質の確認、治験用である旨の表示等（以下「表示等」という。）を行った上、治験依頼者に供給する必要がある場合は、当該コンパニオン診断薬等の名称（販売名、成分名等）、数量、使用目的並びに表示等を行う企業の名称及び住所を治験届の備考欄に記載すること。

イコンパニオン診断薬等のうち医療機器に該当し、治験届が必要なものについては、当該治験届の備考欄にその旨を記載し、関連する医薬品の開発状況について、可能な範囲で簡潔に記載すること。なお、医療機器の治験届が必要とされる範囲については「機械器具等に係る治験の計画等の届出の取扱い等について」（平成25年３月29日付け薬食機発0329第10号厚生労働省医薬食品局審査管理課医療機器審査管理室長通知）を参照すること。

ウ上記アに基づく治験の届出の際には、必要に応じ、PMDA又は厚生労働省医薬食品局審査管理課から医薬品の治験届出者に対してコンパニオン診断薬等の開発状況に関する問い合わせを行う場合があること。

３その他

（１）PMDAの審査体制上記２（１）に関し、同時期に承認申請されたコンパニオン診断薬等及び関連する医薬品については、PMDAにおいて、医薬品の審査担当部とコンパニオン診断薬等の審査担当部との間で、十分な連携を図りながら対応することとし、審査の進行管理等についても必要な調整を図ることとしたこと。あわせて、開発段階の治験相談についても同様に連携を図ることとする。

（２）関連通知の改正

ア「医療機器の製造販売承認申請に際し留意すべき事項について」（平成17年２月16日付け薬食機発第0216001号厚生労働省医薬食品局審査管理課医療機器審査管理室長通知）の記の第２の12の(9)を次のように改める。

⑼ 昭和61年3月12日付薬審2第98号審査第一課長、審査第二課長、生物製剤課長連名通知「注射剤に溶解液等を組み合わせたキット製品等の取扱いについて」のキット製品、平成5年10月1日付薬新薬第92号新医薬品課長、医療機器開発課長、安全課長連名通知「薬事法及び医薬品副作用被害救済・研究振興基金法の一部を改正する法律の施行について」の優先審査対象品目又は平成25年７月１日付薬食審査発0701第10号審査管理課長通知「コンパニオン診断薬等及び関連する医薬品の承認申請に係る留意事項について」に該当する医療機器を申請する場合にはその旨を、また、共同開発により複数の者が申請する場合にはその旨及び他の共同申請者名を記載すること。

イ「体外診断用医薬品の製造販売承認申請に際し留意すべき事項について」（平成17年２月16日付け薬食機発第0216005号厚生労働省医薬食品局審査管理課医療機器審査管理室長通知）の記の第１の11.の12）の次に次のように加える。

13）平成25年７月１日付け薬食審査発0701第10号審査管理課長通知「コンパニオン診断薬等及び関連する医薬品の承認申請に係る留意事項について」に該当する体外診断用医薬品として申請する場合にはその旨を記載すること。

ウ「医薬品の承認申請に際し留意すべき事項について」（平成17年３月31日付け薬食審査発第0331009号厚生労働省医薬食品局審査管理課医療機器審査管理室長通知）の記の６の（6）のウを次のように改める。

ウその他、日本薬局方収載品目、優先審査の適用を受けようとする品目、安定性試験継続中の品目若しくはキット製品を申請する場合又はコンパニオン診断薬等が併せて申請される場合はその旨を、また、共同開発により複数の者が申請する場合には他の共同申請者名を記載すること。

エ「機械器具等に係る治験の計画等の届出の取扱い等について」（平成25年３月29日付け薬食機発0329第10号厚生労働省医薬食品局審査管理課医療機器審査管理室長通知）の別添１の2.の（９）備考を次のように改める。

（９）備考

①届書に添付した資料名を記載すること。

②コンパニオン診断薬等のうち医療機器に該当するものの治験届出にあたっては、その旨を記載し、対応する医薬品の開発状況について、可能な範囲で簡潔に記載すること。また、治験依頼者とは別の企業が当該コンパニオン診断薬等を輸入し、当該企業が品質の確認、治験用である旨の表示等（以下「表示等」という。）を行った上、治験依頼者に供給する必要がある場合は、当該コンパニオン診断薬等の名称（販売名、成分名等）、数量、使用目的並びに表示等を行う企業の名称及び住所を記載すること。

オ「自ら治験を実施しようとする者による薬物に係る治験の計画の届出等に関する取扱いについて」（平成25年５月31日付け薬食審査発0531第４号厚生労働省医薬食品局審査管理課長通知）の別添１の2.の（12）の①中キをクとし、カの次に次のように加える。

キ コンパニオン診断薬等同時開発品

医薬品の治験届出にあたって、対応するコンパニオン診断薬等の開発が行われている場合には、その旨を記載し、当該コンパニオン診断薬等の開発状況について、可能な範囲で簡潔に記載すること。また、治験依頼者とは別の企業が当該コンパニオン診断薬等を輸入し、当該企業が品質の確認、治験用である旨の表示等（以下「表示等」という。）を行った上、治験依頼者に供給する必要がある場合は、当該コンパニオン診断薬等の名称（販売名、成分名等）、数量、使用目的並びに表示等を行う企業の名称及び住所を記載すること。

カ「治験の依頼をしようとする者による薬物に係る治験の計画の届出等に関する取扱いについて」（平成25年５月31日付け薬食審査発0531第８号）の別添１の2.の（12）中⑦を⑧とし、⑥の次に次のように加える。

⑦コンパニオン診断薬等同時開発品

医薬品の治験届出にあたって、対応するコンパニオン診断薬等の開発が行われている場合には、その旨を記載し、当該コンパニオン診断薬等の開発状況について、可能な範囲で簡潔に記載すること。また、治験依頼者とは別の企業が当該コンパニオン診断薬等を輸入し、当該企業が品質の確認、治験用である旨の表示等（以下「表示等」という。）を行った上、治験依頼者に供給する必要がある場合は、当該コンパニオン診断薬等の名称（販売名、成分名等）、数量、使用目的並びに表示等を行う企業の名称及び住所を記載すること。

（３）適用時期

対応するコンパニオン診断薬等の開発が行われている薬物に係る治験届の取扱いについては、平成26年２月１日以降に新たに届出される治験計画届書に適用する。

また、その他の取扱いについては、平成26年７月１日以降に承認申請される医薬品及びコンパニオン診断薬等について適用する。なお、平成25年７月１日以降、本通知に基づき治験の届出又は承認申請を行って差し支えないこと。