Provisional Translation (as of December 2025)*

Evaluation Report on Applicability to Drug-agnostic Companion Diagnostics

August 29, 2025
Pharmaceuticals and Medical Devices Agency

1. Proposer
The Japan Lung Cancer Society

2. Candidate products (as per order in proposal)

Product 1	Brand name	Cobas EGFR mutation test v2.0
	Approval No.	22800EZX00011000
	Marketing authorization holder	Roche Diagnostics K.K.
Product 2	Brand name	Oncomine Dx Target Test Multi-CDx System
	Approval No.	23000BZX00089000
	Marketing authorization holder	Life Technologies Japan Ltd.
Product 3	Brand name	therascreen EGFR RGQ PCR kit “QIAGEN”
	Approval No.	22300AMX01256000
	Marketing authorization holder	Qiagen K.K.
Product 4	Brand name	FoundationOne CDx cancer genome profile
	Approval No.	23000BZX00403000
	Marketing authorization holder	Chugai Pharmaceutical Co., Ltd.
Product 5	Brand name	EGFR LIQUID gene analysis software
	Approval No.	30200BZX00249000
	Marketing authorization holder	DNA Chip Research Inc.
Product 6	Brand name	AmoyDx Pan Lung Cancer PCR Panel
	Approval No.	30300EZX00076000
	Marketing authorization holder	Riken Genesis Co., Ltd.
Product 7	Brand name	Lung Cancer Compact Panel Dx Multiplex Companion Diagnostic System
	Approval No.	30400BZX00263000
	Marketing authorization holder	DNA Chip Research Inc.

* This English version of the Japanese Notification is provided for reference purposes only.
In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

3. Outline of the submitted proposal and summary of examination at the Pharmaceuticals and Medical Devices Agency

(1) Background of submission of the proposal

Because the products listed in 2. meet Requirements (1) to (3) below based on the "Notification on Handling of In Vitro Diagnostics and Medical Device Products Aiming for Drug-agnostic Companion Diagnosis" (PSEHB/PED Notification No. 0331-1, PSEHB/MDED Notification No. 0331-1, PSEHB/PSD Notification No. 0331-1, dated March 31, 2022) (hereinafter referred to as "Drug-agnostic Use Notification"), a proposal to handle these products as drug-agnostic CDx was submitted.

Requirement (1)	More than one CDx product with the same intended use (i.e. the target disease (cancer type in the case of malignant tumors), biomarker and specimen type) is approved.
Requirement (2)	Therapeutic product(s) for which each CDx product is approved to be used as aid in identifying the eligible patients for treatment is (are) different.
Requirement (3)	It is considered scientifically reasonable to use the test results of any of the CDx products interchangeably to identify the eligible patients for treatment with relevant therapeutic products.

In the proposal, the Japan Lung Cancer Society (hereinafter referred to as the "JLCS") explained use status of companion diagnostics (hereinafter referred to as "CDx") that are used as aid in identifying eligible patients for drugs approved for the indication of *EGFR* mutation-positive non-small cell lung cancer (hereinafter referred to as "EGFR molecular target drugs") and issues with them in clinical practice as follows.

Because each of EGFR molecular target drugs has characteristic indications and adverse reactions, and according to detected *EGFR* mutations, EGFR molecular target drugs are selected for use, CDx is used before the selection of EGFR molecular target drugs. However, if the CDx used does not correspond to EGFR molecular target drugs which are considered appropriate based on the detected mutations, the molecular target drugs cannot be used within the scope of health insurance, raising a concern that appropriate treatment may not be provided to patients.

To address the above issue, the JLCS proposed that CDx products for detection of *EGFR* mutations in non-small cell lung cancer tissues be used in a drug-agnostic manner, regardless of which EGFR molecular target drugs they are approved as aid in identifying eligible patients for. The society additionally explained the proposal of excluding the CDx products using plasma samples for detection of *EGFR* mutations from the scope of drug-agnostic use, because study results for correlation between tests using plasma samples and those using tissue samples are difficult to interpret, and the detection limit differs between the tests. Products 1 and 5 are available for use with both tissue and plasma samples, but the proposed scope of drug-agnostic use included them only when using tissue samples. The society further explained that exon 20 insertion was excluded from the biomarkers subject to the proposal, because there are no approved EGFR molecular target drugs potentially indicated based on this mutation, and analytical equivalence among the products for this biomarker has not been adequately evaluated.

(2) Proposal on applicability to the requirements for drug-agnostic CDx

The JLCS explained the applicability to each requirement provided in the Drug-agnostic Use Notification as follows.

The products in this proposal, which have been approved as presented in Table 1, meet Requirements (1) and (2).

Table 1 Combinations of candidate products and corresponding EGFR molecular targeted drugs

	Gefitinib	Erlotinib hydrochloride	Afatinib maleate	Osimertinib mesilate	Dacomitinib hydrate
Product 1	○	○	○	○	○
Product 2	○	○	○	○	○
Product 3	○	○	○	×	○
Product 4	○	○	○	○	○
Product 5	○	○	○	×	×
Product 6	○	○	○	○	×
Product 7	○	○	○	○	×

The society explained the applicability to Requirement (3) as follows:

Equivalence among the products can be evaluated based on study results provided in the package inserts (see Table 2). FFPE samples were used except for Product 5, which used unfixed tissue samples. Numerical values in Table 2 were directly transcribed from the package inserts, because companies used different significant figures in the studies. Control methods were also directly transcribed from the package inserts, including ones of which details were unclear.

Table 2 Study results for concordance provided in the package inserts of the products

	Control method	Number of samples	Positive percent agreement	Negative percent agreement
Product 1	Company A real-time PCR method[*1]	118	100%	98%
	Company B real-time PCR method[*1]	118	100%	100%
	Cobas EGFR mutation test kit[*2]	369	96.6%	96.3%
	NGS method	368	88.3%	97.3%
Product 2	Real-time PCR method-1[*3]	119	100%	95.2%
	Real-time PCR method-2[*4]	193	98.6%	99.2%
Product 3	Sanger sequencing	360	99.4%	86.6%
	Previous-generation product	192	97.09%	97.75%
Product 4	Approved product A (PCR method)[*5]	262	98.1%	99.4%
	Approved product A (PCR method) and Approved product B (PCR method)[*6]	129	97.2%	100%
	Approved product A (PCR method) and Approved product C (PCR method)[*7]	196	98.9%	86.1%

Product 5	PNA-LNA PCR clamp method[*8]	156	88.2%	100%
Product 6	Company A PCR test kit[*9]	226	99.4%	96.6%
	Company B NGS test	334	100%	98.5%
Product 7	Approved in vitro diagnostics (PCR method)[*10]	150	100%	90.9%

*1 Because dacomitinib hydrate was added to potentially indicated drugs after the initial approval, Company A or B real-time PCR method is considered Product 3.

*2 Previous-generation product of Product 1. Correlation study only for T790M mutation

*3 Correlation study for exon 19 deletion and L858R mutations Because the control method was selected based on its regulatory status, being approved as CDx for drugs including osimertinib mesilate, it is considered Product 1.

*4 Because the control method was selected based on its regulatory status, being approved as CDx for dacomitinib hydrate, it is considered Product 3.

*5 Correlation study for exon 19 deletion and L858R mutations Because the control method was selected based on its regulatory status, being approved as CDx for drugs including osimertinib mesilate, it is considered Product 1.

*6 Correlation study for exon 19 deletion and L858R mutations Because the control method was selected based on its regulatory status, being approved as CDx for dacomitinib hydrate, Approved product A or B is considered Product 3.

*7 Correlation study for T790M mutation Because the control method was selected based on its regulatory status, being approved as CDx for drugs including osimertinib mesilate, Approved product A or C is considered Product 1 or Cobas EGFR mutation test kit.

*8 Correlation study for exon 19 deletion and L858R mutations

*9 Because the control method was selected based on its regulatory status, being approved as CDx for drugs including osimertinib mesilate, it is considered Product 1.

*10 The literature[1] listed in the package insert states that the control method is Product 1.

For a follow-on CDx developed following the original CDx, which has been developed in association with clinical studies of drugs, clinical performance should be evaluated based on its equivalence to the original one. Of CDx products used as an aid in identifying eligible patients for osimertinib mesilate and/or dacomitinib hydrate, ones approved after issuance of the "Notification on Approval Application for In Vitro Companion Diagnostics and Corresponding Therapeutic Products" (PFSB/ELD Notification No. 0701-10, dated July 1, 2013) must have been evaluated for their equivalence to Product 1 and/or Product 3, respectively, and the study results are assumed to be included in the package insert. On the above assumption, equivalence among the products except for Product 5 is considered to have been demonstrated, based on study results in Table 2.

For Product 5, a correlation study for detection of *EGFR* mutations was conducted using PNA-LNA PCR clamp method. The PNA-LNA PCR clamp method was used for enrollment of patients in a phase III clinical study of gefitinib[2] and is a laboratory developed test that can be covered by health insurance. In addition, because a considerable literature has reported equivalence of the PNA-LNA PCR clamp method to Products 1, 2, and 3, Product 5 approved based on the equivalence to the PNA-LNA PCR clamp method is also considered to be analytically equivalent to the other products.

For T790M mutation, some products have not been demonstrated to be equivalent to Product 1, but for the other single base substitutions such as L858R mutation, they have been demonstrated to be equivalent in terms of detection performance. Their drug-agnostic use would have no practical problems on the condition that caution about the minimum detection sensitivity, which is described

below, is raised.

For others, equivalence among the products and equivalence of each product to the standard test method were explained based on the peer-reviewed literature.

The JLCS reviewed the following 4 points for risk minimization measures in clinical settings in view of differences among CDx products.

1) Exclusion of exon 20 insertion mutation from drug-agnostic CDx use

The exon 20 insertion mutation has been reported to have at least 100 patterns and also known to be widely diverse in terms of the drug effect.[3] Six PCR-based tests including Products 1 and 3 are not originally designed to cover the exon 20 insertion mutation adequately, yielding the detection rates of 11.8% to 58.9%.[4] Based on the above, the exon 20 insertion mutation should not be included in the scope of the drug-agnostic CDx in this document and thus should be separately considered.

2) Differences of *EGFR* mutations to be detected

Because products cover different detectable ranges of *EGFR* mutations, they should be used in view of their ranges. For detectable ranges of *EGFR* mutations and the impact of the compound mutation status, the JLCS plans to raise caution in the "Guidance for Biomarker Tests in Patients with Lung Cancer" (hereinafter referred to as "Guidance for Tests").

3) Limit of detection

Because products have different minimum detection sensitivities, they should be used with full understanding of their characteristics. For representative *EGFR* mutations, the limits of detection provided in the package insert of each product are as shown below. For test samples, descriptions were directly transcribed from the package inserts, although they were not standardized in terms of format among companies. Numerical values were directly transcribed from the package inserts, because companies used different significant figures in the studies. Only for Product 3, the minimum detection sensitivity was calculated by regression analysis, but not by the hit rate method.

Table 3 Limits of detection provided in the package insert of each product

	Test samples	L858R mutation	Exon 19 deletion mutation	T790M mutation
Product 1	FFPE tissue sample	3.96 to 5.32%	1.39 to 2.53%	2.04 to 3.03%
Product 2	Non-small cell lung cancer sample	5.3%	4.4%	5.7%
Product 3	Cell lines, plasmids, and clinical samples	5.94% (cell line)	0.14% to 16.87% (sample type differs for each mutation)	9.72% (cell line)
Product 4	No description	2.4%	5.1%	2.5%
Product 5	No description[*1]			Outside detection targets
Product 6	Control substance for sensitivity test	1%	1%	2%
Product 7	No description	No description	No description	No description

*1 The Precautions section in the package insert includes a cautionary statement that because exon 19 deletion mutation and L858R mutation with allele frequency of <5% are detected in tissue specimens, a population in which efficacy and safety have not been evaluated in clinical studies of candidate drugs may test positive.

For Product 7, the literature[1] listed in the package insert reported that 24 samples with the allele frequency of exon 19 deletion, L858R, or T790M mutation adjusted to 1% were prepared from the Horizon Discovery's standard and wild-type lung tissues and evaluated for sensitivity, and false negative occurred in 0% (0 of 24) of samples, suggesting that the minimum detection sensitivity would be 1% or lower. Actually, another report[5] showed that the limits of detection for L858R, exon 19 deletion, and T790M mutations were 0.20%, 0.14%, and 0.48%, respectively.

Based on results in Table 3, the minimum detection sensitivity differs among products, particularly for deletion mutations. In addition, if presence or absence of T790M mutation is checked for the second-line treatment in patients who have received a first- or second-generation EGFR molecular target drug, a CDx product should be selected with reference to the minimum detection sensitivity of Product 1 which was developed in association with clinical studies. For the above precautions for use, the JLCS plans to raise caution via the Guidance for Tests, etc. The JLCS will request marketing authorization holders and related companies to provide information about the minimum detection sensitivity and its assessment method if they have not provided the information concerned in the package insert, etc.

4) Discordance cases

Products may yield discrepant results because of differences in mutations to be detected and a relationship between the percentage of tumor cells in the sample and the minimum detection sensitivity. Such discordance is inevitable because test methods used in the products differ in detection principle and characteristics, but reliability of the test results is critical to patients in determining treatment strategies. The JLCS plans to adequately raise caution about potential discrepancies arising from differences of test methods and extensively inform healthcare professionals of other test methods covered by the current health insurance (e.g., active use of comprehensive genomic profiling). For discordance cases, causes should be investigated, and the test methods should be fully characterized and understood.

(3) Summary of evaluation at the Pharmaceuticals and Medical Devices Agency

The Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") has presented the principles for applicability to drug-agnostic CDx in the "Guidance on Drug-Agnostic Companion Diagnostics" (PMDA Notification No. 0628013, dated June 28, 2022) (hereinafter referred to as the "Guidance Notification") based on the Drug-agnostic Use Notification. PMDA's conclusion in view of the comments from the Expert Discussion is as follows:

The expert advisors at the Expert Discussion on this proposal declared that it does not fall under Section 4 of the "Rules for Convening Expert Discussions, etc. by the Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1) Differences in *EGFR* mutations to be analyzed

The Guidance Notification describes that "For CDx that detects multiple variants of a specific gene, it is assumed that there may be cases in which variants to be detected are not completely the same between products. In such cases, if the equivalence studies using specimens from the typical patient population subject to the corresponding drug demonstrate a high percentage of concordance between

CDx products, and the differences between products are recognized only in rare variants that are detected infrequently in the target patients, these CDx products are considered to meet Requirement (3).” Exon 19 deletion and L858R mutations, which are described as common mutations in the Guidance for Tests of the JLCS, are detectable in all products. However, Product 5 cannot detect G719X, S768I, or L861Q mutation, any of which is described as uncommon mutation, and the other products cannot detect a part of the uncommon mutations, such as E709X mutation, either. If the Guidance for Tests raises caution about detectable ranges of *EGFR* mutations, as proposed by the JLCS, PMDA considers that a concern about uncommon mutations and compound mutations would not be a major problem.

The T790M mutation can be detected with products other than Product 5. On the other hand, equivalence of detection performance only for T790M mutation has been evaluated in the limited number of studies, and the equivalence among all products has not been evaluated, as shown in the equivalence study results in Table 2 and other literature. Because the T790M mutation is becoming recognized as a biomarker as with the other mutations; and equivalence of detection performance for the T790M mutation, which is a single base substitution, has not been thoroughly evaluated, but such equivalence for the other single base substitutions has been demonstrated, PMDA considers that this mutation may be included in the scope of drug-agnostic use, as proposed by the JLCS, on the condition that caution about limits of detection, etc. be raised. Of note, for Products 2 and 3 which have the minimum detection sensitivity for the T790M mutation lower than that of Product 1, the original CDx, relevant cautionary statement must be included in the package insert.

On the other hand, exon 20 insertion mutation should not be included in the scope of drug-agnostic use, as proposed by the JLCS, because they are diverse, and the equivalence has not been evaluated. In addition, an EGFR molecular target drug potentially indicated based on presence or absence of exon 20 insertion mutation has been approved. Before use of drug-agnostic CDx for the concerned mutation, users should refer to the PMDA’s website and the Guidance for Tests of the JLCS to check the range of variants eligible for drug-agnostic CDx and identify products including the concerned mutation in their range of detection, and then select CDx according to their purpose. Because biomarker tests for treatment of lung cancer are widely used in clinical practice, the above procedure for selecting necessary CDx with reference to the Guidance for Tests of the JLCS is considered to have no particular problem.

2) Evaluation of equivalence among products

The Guidance Notification describes that applicability will be evaluated based on the percentages of concordance in an equivalence study among approved CDx products. PMDA has no objection to the proposal of the JLCS, allowing drug-agnostic use based on results in Table 2. Product 5 covers only limited mutations for detection and uses a different type of samples from those for the other products. In addition, its equivalence to other products has not been evaluated directly. However, in view of the proposal of the JLCS and the above review, PMDA considers it acceptable to include Product 5 in the scope of drug-agnostic use based on information available to date in the public domain. The expert advisors supported the concerned policy. As proposed by the JLCS, information about the minimum detection sensitivity needs to be provided, and thus marketing authorization holders of the products should proceed with marketing in appropriate cooperation with the JLCS.

4. Regulatory procedures for marketing products as drug-agnostic CDx

On the basis of the above review, PMDA concluded that 7 products proposed by the JLCS fall under drug-agnostic CDx. For Products 1, 3, and 6, which are in vitro diagnostics, the Intended Use may be

amended as follows, on the condition that the "Important Precautions" section of the package insert include the statements presented below.

Intended Use
Detection of *EGFR* mutations in DNA samples extracted from cancer tissues (to be used as aid in identifying eligible patients with non-small cell lung cancer for EGFR molecular target drugs)

Important Precautions
- Before performing EGFR test with the product, refer to guidelines, etc. of related academic societies.
- Before using the product as an aid in identifying eligible patients for EGFR molecular target drugs, be well informed of and understand details of reports for drug-agnostic use. The reports for drug-agnostic use and information about drugs for which eligible patients can be identified by drug-agnostic CDx are available at the following website.
  (website address of the Companion Diagnostics WG)
- (Product 3 only) It should be noted that the product has the detection sensitivity for *EGFR* T790M mutation lower than that of the test method used in clinical studies of osimertinib mesilate and thus may yield false negative results.

For Products 2, 4, 5, and 7, which are medical devices, the Intended Use or Indication may be amended as follows, on the condition that the "Precautions Concerning Intended Use or Indication" section of the package insert include the statements presented below.

Intended Use or Indication
- A biomarker to be detected is defined as "*EGFR* mutations."
- The corresponding drugs are "EGFR molecular target drugs."

Precautions Concerning Intended Use or Indication
- Before performing EGFR test with the product, refer to guidelines, etc. of related academic societies.
- Before using the product as an aid in identifying eligible patients for EGFR molecular target drugs, be well informed of and understand details of reports for drug-agnostic use. The reports for drug-agnostic use and information about drugs for which eligible patients can be identified by drug-agnostic CDx are available at the following website.
  (website address of the Companion Diagnostics WG)
- (Product 2 only) It should be noted that the product has the detection sensitivity for *EGFR* T790M mutation lower than that of the test method used in clinical studies of osimertinib mesilate and thus may yield false negative results.

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【References】

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2. Maemondo M, et al., “Gefitinib or chemotherapy for non–small-cell lung cancer with mutated EGFR.” New Eng. J. Med., 2010, 362, 2380. (doi: 10.1056/NEJMoa0909530.)

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【List of Abbreviations】

CDx	Companion Diagnostics
EGFR	Epidermal Growth Factor Receptor
FFPE	Formalin Fixed Paraffin Embedded
LNA	Locked Nucleic Acid
NGS	Next-generation sequencer
PCR	Polymerase Chain Reaction
PNA	Peptide Nucleic Acid