Determining the Path for Assessment of a Companion Diagnostic (CDx) under the *In Vitro* Diagnostic Medical Devices Regulation

Introduction

In May 2017, the Regulations on *in vitro* diagnostic medical devices entered into force in Europe: Regulation 2017/746 on in vitro diagnostic medical devices (IVDR). This regulation will fully replace IVDD (98/79/EC) after a transitional period of 5 years (Date of Application: 26 May 2022).

The adoption of this regulation marks a significant development and strengthening of the existing regulatory framework for *in vitro* diagnostics in Europe and will replace the original Directive, which has been in place for over 20 years.

The new IVDR has significant implications for the regulation of companion diagnostics.

Under IVDR, companion diagnostics will be classified as Class C devices (the second highest risk level) and the corresponding conformity assessment will necessitate interaction with both a Notified Body and the European Medicines Agency (EMA)/National Competent Authorities (NCAs). This regulation makes the first European regulatory link between approval of the medicine and the companion diagnostic.

While the IVDR sets out the expectations for companion diagnostics with an associated medicine, there is still a level of uncertainty on how the regulation will be implemented. As such, guidance and clarification are required. In addition, guidance on the route for the re-certification of *in vitro* diagnostics already utilised to guide treatment decisions will also be required; additional information and guidance on the path for follow-on diagnostics (new diagnostic tests for existing precision medicines already on the EU Market that were originally approved with a CDx test) will also be essential.

In this document, EFPIA and MedTech Europe set out several key areas of uncertainty relating to the regulation of companion diagnostics and the associated medicinal product. For each area of uncertainty, specific proposals for consideration are also laid out.

In addition, EFPIA and MedTech Europe have identified concerns among medicinal product and IVD manufacturers; specifically, that there will be an insufficient number of Notified Bodies designated under IVDR to conduct the required reviews of IVDs requiring re-assessment, including diagnostics currently used to select patients for treatment. A delay to implementation of IVDR would be required in order to ensure that sufficient preparation is made to enable successful implementation of the new regulation.

About EFPIA

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. Through its direct membership of 36 national associations and 39 leading pharmaceutical companies, EFPIA's mission is to create a collaborative environment that enables our members to innovate, discover, develop and deliver new therapies and vaccines for people across Europe, as well as contribute to the European economy. Our vision is for a healthier future for Europe. A future based on prevention, innovation, access to new treatments and better outcomes for patients.

About MedTech Europe

MedTech Europe is the European trade association for the medical technology industry including diagnostics, medical devices and digital health. Our members are national, European and multinational companies as well as a network of national medical technology associations who research, develop, manufacture, distribute and supply health-related technologies, services and solutions.

List of Abbreviations and Glossary of Terms

Most of the following list of abbreviations and glossary of terms are taken from Article 2 (Definitions) from the IVDR. Additional items in the list of abbreviations and glossary of terms which are not included in Article 2 (Definitions) of the IVDR are also defined here.

Abbreviation	Explanation
AIMDD	Active Implantable Medical Device Directive, 90/385/EEC, covers the placing on the market and putting into service of active implantable medical devices
Analytical performance	Analytical performance means the ability of a device to correctly detect or measure a particular analyte
Benefit-risk determination	Benefit-risk determination means the analysis of all assessments of benefit and risk of possible relevance for the use of the device for the intended purpose, when used in accordance with the intended purpose given by the manufacturer
CAMD	Competent Authorities for Medical Devices (CAMD)
CE Marking	'CE marking of conformity' or 'CE marking' means a marking by which a manufacturer indicates that a device is in conformity with the applicable requirements set out in this Regulation and other applicable Union harmonisation legislation providing for its affixing
CHMP	Committee for Medicinal Products for Human Use
Clinical performance	'Clinical performance' means the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user
Companion Diagnostic (CDx)	A companion diagnostic is defined for the first time in Europe in the IVD Regulation 2017/746/EU, Article 2(7): "companion diagnostic' means a device which is essential for the safe and effective use of a corresponding medicinal product to: a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product"
Conformity assessment	Conformity assessment means the process demonstrating whether the requirements of this Regulation relating to a device have been fulfilled
Conformity assessment body	Conformity assessment body means a body that performs third-party conformity assessment activities including calibration, testing, certification and inspection
CTA	Clinical Trial Application
Devices manufactured and used only within healthcare institutions	Commonly referred to in other jurisdictions as laboratory developed test (LDT) or in-house devices. Requirements for these are given in Reference Chapter II Article 5 of the IVDR These devices will not be dealt with further in the scope of the document
DHF	Design History File

Abbreviation	Explanation
EAP	Early Access Program - These are country-specific regulatory tools that allow a drug to be available on the market before its official launch, providing that it fulfils specific criteria
EC	Ethics Committee
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations. EFPIA is a Brussels-based trade association founded in 1978 representing the research-based pharmaceutical industry operating in Europe
EMA	European Medicines Agency
EU	European Union
EUDAMED	European Database on Medical Devices
FDA	Food and Drug Administration. FDA is an agency of the United States Department of Health and Human Services, one of the United States federal executive departments, responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), veterinary products and cosmetics
Follow-on tests	Follow-on tests are new CDx tests for use with existing precision medicines already on the EU Market. The medicinal product was originally approved with a different CE-marked CDx test, typically the one used during the pivotal prospective clinical trial for the medicinal product
GCP	Good Clinical Practice is an international quality standard that is provided by International Conference on Harmonization (ICH), an international body that defines standards, which governments can transpose into regulations for clinical trials involving human subjects. Good Clinical Practice guidelines include protection of human rights as a subject in clinical trial, assurance of the safety and efficacy of the newly developed compounds and standards on how clinical trials should be conducted
Grandfather clause (or Grandfather policy or Grandfathering)	A grandfather clause (or grandfather policy or grandfathering) is a provision by which an old rule continues to apply to some existing situations while a new rule will apply to all future cases. Those exempt from the new rule are said to have grandfather rights or acquired rights, or to have been "grandfathered in"
HA/HAs	Health Authority/Health Authorities
HTA	Health Technology Assessment
Instructions for use	Instructions for use means the information provided by the manufacturer to inform the user of a device's intended purpose and proper use and of any precautions to be taken
Intended purpose	Intended purpose means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements or as specified by the manufacturer in the performance evaluation
ISO	International Organization for Standardization
ISO 13485	ISO 13485 is a published ISO standard that represents the requirements for a comprehensive quality management system for the design and manufacture of medical devices

Abbreviation	Explanation
ISO 9001	ISO 9001 is an ISO standard that represents the requirements for quality management systems. It is used across industries and is not specific to medical devices like ISO 13485
***In vitro* diagnostic medical device (IVD)**	*In vitro* diagnostic medical device means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following: (a) concerning a physiological or pathological process or state; (b) concerning congenital physical or mental impairments; (c) concerning the predisposition to a medical condition or a disease; (d) to determine the safety and compatibility with potential recipients; (e) to predict treatment response or reactions; (f) to define or monitor therapeutic measures. Specimen receptacles shall also be deemed to be *in vitro* diagnostic medical devices
IVDD	*In Vitro* Diagnostic Directive. The Council Directive 98/79/EC on *In Vitro* Diagnostic Medical Devices (IVDD) (1998) delineates requirements that *in vitro* diagnostic devices must meet before they can be sold in the EU market
IVDR	*In Vitro* Diagnostic Regulation. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU
Label	Label means the written, printed or graphic information appearing either on the device itself, or on the packaging of each unit or on the packaging of multiple devices
LoOI	List of outstanding issues
MAH	Marketing Authorisation Holder (MAH) is a company, firm or non-profit organisation that has been granted a marketing authorisation. The marketing authorisation allows the holder to market a specific medicinal product, in one or more EU member states. The use of the medicinal product is linked to the related CDx device as specified in the SmPC
MDCG	Medical Device Co-ordination Group. MDCG provides advice to the Commission and assists the Commission and the Member States in ensuring a harmonised implementation of medical devices Regulations (EU) 2017/745 and 2017/746
MDD	The Medical Device Directive is intended to harmonize the laws relating to medical devices within the European Union. Council Directive 93/42/EEC on Medical Devices (MDD) was most recently reviewed and amended by 2007/47/EC and a number of changes were made. Compliance with the revised directive became mandatory on March 21, 2010
Medicinal product label/labelling	Medicinal product label/labelling refers to the information included in the Summary of Product Characteristics (SmPC) and Package Leaflet (PL)
MPSV	German Safety Plan for Medical Devices of the German Medical Device Act [MPG]

Abbreviation	Explanation
MPKPV	Verordnung über klinische Prüfung von Medizinprodukten of the German Medical Device Act [MPG]
MDR	Medical Device Regulation. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices, amending Directive 2001/83/EC, Regulation EC No 178/2002 and regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
MedTech Europe (MTE)	MedTech Europe is the European trade association representing the medical technology industries, from diagnosis to cure. It represents Diagnostics and Medical Device manufacturers operating in Europe
NCA	National Competent Authority. The national competent authorities are primarily responsible for the authorisation of medicines available in the EU that do not pass through the centralised procedure
Notified Body	A Notified Body, in the European Union, is a conformity assessment body that has been designated/notified by a Member State to assess whether a product meets certain preordained standards or regulations. Assessment can include inspection and examination of a product, its design and manufacture
PL	Package leaflet - the leaflet in every pack of medicine that contains information on the medicine for end-users, such as patients
Performance evaluation	Performance evaluation means an assessment and analysis of data to establish or verify the scientific validity, the analytical and, where applicable, the clinical performance of a device
Performance study	Performance study means a study undertaken to establish or confirm the analytical or clinical performance of a device
Placing on the market	Placing on the market means the first making available of a device, other than a device for performance study, on the European Union market
PMPF	Post-Market Performance Plan
PRIME	Priority medicines scheme. It is a voluntary scheme launched by the European Medicines Agency to enhance support for the development of medicines that target an unmet medical need. It is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier
QA	Quality Assurance refers to a program for the systematic monitoring and evaluation of the various aspects of a project, service, or facility to ensure that standards of quality are being met
QMS	Quality Management System can be expressed as the organizational structure, procedures, processes and resources needed to implement quality management. A QMS is also used to ensure compliance with relevant regulations such as IVDR
Risk	Risk means the combination of the probability of occurrence of harm and the severity of that harm
SmPC	Summary of Product Characteristics - a document describing the properties and the officially approved conditions of use of a medicine. Summaries of product characteristics form the basis of information for healthcare professionals on how to use the medicine safely and effectively
SOP	Standard Operating Procedure
US	United States

Abbreviation	Explanation
Validation	Validation is defined as the documented act of demonstrating that a procedure, process and/or activity will consistently lead to the expected results. It often includes the qualification of systems and equipment. It is a requirement for Good Manufacturing Practices and other regulatory requirements

Questions and Position Statements

1	**How will companies be able to seek voluntary scientific advice on the path to medicinal product/companion diagnostic co-development, submission and approval?** ○ **How will dialogue with National Competent Authorities (NCA)/European Medicines Agency (EMA) and Notified Bodies (NB) be conducted?** ○ **What will the roles and responsibilities for each party be?**
	Background The registration pathways for medicinal products and diagnostic tests are independent of each other in the European Union. This may lead to the lack of coordination between multiple EU institutions like the EMA including the Committee for Medicinal Products for Human Use (CHMP), National Competent Authorities (NCA) for both medicinal products and devices and Notified Bodies (NBs). Opinion of the ethics committee (EC) is an established national process as part of the devices study approval and should also be considered. Such lack of coordination could pose a significant challenge for medicine developers and diagnostic manufacturers during the development and registration of the medicinal product and its associated companion diagnostic test, thereby delaying or hampering the availability of such a product and test on the European market. Position Statement In some jurisdictions, a co-development approach includes an effective and early means for consultation to obtain collaborative joint advice, which can ensure an efficient development and subsequent review of the medicinal product and its associated companion diagnostic. The EU system should strive to gain knowledge from the lessons learnt from such systems and understand the key success factors required to emulate these processes. Of key importance is that the advice provided should be jointly agreed upon by the medicinal product regulatory agency (EMA or NCA) and the appropriate Notified Body (NB) or Device Competent Authority. The advice provided should seek to clarify and agree the proposed development program timings and interdependencies, as well as the evidentiary requirements of all agencies. Advice should be available, where requested by the applicant, very early in development on aspects such as biomarker qualification and development and should be considered good practice prior to the pivotal clinical trials (though the procedure should remain voluntary). While an overall programmatic process should govern the responsibilities of each party during the co-assessment and review processes, the advice provided should also clarify in greater detail how the process will work for the specific products and reviewers involved. The following actions are required to enable a fit for purpose approach: • A joint pre-submission advice and consultation process should allow for a collaborative approach between the EMA/NCA and NBs and/or National Competent Authority for Devices. This procedure would strive to be a 'joint' process with a goal of providing developers with a single agreed-upon clinical development plan appropriate for both the companion diagnostic and the medicinal product. This procedure would be in addition to and complement any separate scientific advice procedures specific to the medicinal product or diagnostic.

	• The EMA should be responsible for administration and co-ordination as a centralized body. The European Commission should encourage other potential participants, such as Notified Bodies, to have adequate resources and be available to support the procedures in a sustainable way. Such a procedure should not exclude the possibility of including other stakeholders if appropriate. • In this joint procedure, it is critical that the right stakeholders are involved and empowered to provide meaningful advice as far as possible within their legal remit. From the Industry side, consider both the medicinal product and companion diagnostic developers as participants, as needed. The EMA or NCA and Notified Body should be present and, if appropriate, a representative from a Device National Competent Authority. Currently, Notified Bodies are restricted in terms of providing advice and consultation to industry. The European Commission should outline how Notified Bodies can participate in a co-development joint pre-submission advice and consultation process, in order to streamline the future joint assessment and co-review process as much as possible. This might involve focusing their formal role on alignment of future review timelines and responsibilities, while enabling further participation in the advice process and dialogue as observers. • Future guidance provided by the authorities should ensure that it outlines information on how such joint pre-submission advice and consultation could be facilitated. This is required urgently to support products already in development which will be reviewed under the IVDR**.** This guidance should also clearly define the objectives and key outputs of the advice (as outlined above) as well as the procedural aspects and timelines. Advice to industry on the correct timing to seek advice should also be provided. • Other existing procedures which may enhance scientific advice support for co-development should be referenced within the guidance, such as the EMA qualification procedure. The PRIME procedure could also be adapted for those products that are eligible. • Where possible, alignment on discussions with the FDA and other Health Authorities (HAs) would be beneficial to enable global development plans. • Another option for consideration would be to have close collaboration with NBs in the qualification procedure while ensuring that overall accountability for the assessment resides with EMA. <u>EFPIA/MedTech Europe Request</u> As outlined above, EFPIA/MedTech Europe would like to propose that: • Appropriate guidance should be developed as soon as possible by the EMA together with NBs, the Medical Device Co-ordination Group (MDCG), the European Commission and other stakeholders (including medicinal product and diagnostic developers) to outline a joint pre-submission advice and consultation procedure. Where possible alignment on discussions with other regulators (including the FDA), should be considered. • Other existing procedures which may enhance scientific advice support for co-development should be considered within the guidance. • Where possible during the co-development process, the EMA should align as far as possible with other global regulators in the advice provided in order to enable global development plans.

2	**How will the National Competent Authority (NCA)/European Medicines Agency (EMA) interact with Notified Bodies (NB)?**
	Background In the case of a co-developed CDx and corresponding medicine, the ideal situation would be to align development timelines and regulatory approvals of both products. The interactions of the medicines authority and NBs would work best if the processes were aligned beginning early in development; however, development of a CDx and a corresponding medicine is often done independently and to different schedules and regulatory requirements. There should, therefore, be provisions for closer working of medicinal product authorities and NBs. For example, it is critical that there is opportunity, where desired, for joint pre-submission advice and consultation (discussed under question 1) so there is clear understanding of the different requirements and expectations for the CDx and medicine respectively by all parties, with joint agreement on a single integrated development plan. This is necessary, as the benefit-risk profile of the medicine depends on the performance of the associated CDx and close co-operation between the NB and the medicinal product authority will be needed. A joint development plan will aid the subsequent co-review of the CDx. It would also be helpful for all parties to have guidance identifying the alignment of the phases in the co-development of assays and medicinal products, considering the different scenarios that are possible for a companion diagnostic (co-development, follow-on to existing IVD already on the market, 2nd generation companion diagnostic, etc). During the conformity assessment process for the CDx, the NCA/EMA will be asked to provide an opinion on the suitability of the device in relation to the medicinal product concerned. EMA/NCA will be consulted by the NB to support the clinical evidence evaluation of the CDx in relation to the medicinal product concerned. Article 48 of IVDR states that NBs shall consult the EMA/NCAs for the medicinal product as described in section 3 (k) of Annex X. This section provides an outline of the process, but practical details of how this will be done are further needed. Position Statement As a first step, Industry asks for the inclusion of information in the 'Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)' document and the Competent Authorities for Medical Devices (CAMD) frequently asked questions (FAQ) document on IVDR. Transitional provisions addressing issues on the pathway for the EMA/NCAs and NB co-review process, including details of the roles and responsibilities, the processes for interaction between EMA/NCAs and NBs, as well as timing of the various assessments (i.e. define the "how and when to interact/align") are requested. The question and answer information should include clarification of how relevant information from the assessment of the CDx will be shared with EMA/NCAs during the medicinal product approval process, as well as how the EMA/NCA opinion will be incorporated back into the CDx assessment process, including when assessment of the diagnostic by NB and EMA/NCA are done in parallel. The Q&A document should include the following considerations: General • The process should be flexible and fit for purpose.

Content:

- Whereas the NB reviews the entire technical documentation dossier for the companion diagnostic, both the notified body and the medicinal products authority will review the suitability of the CDx in relation to the medicinal product. Otherwise, the process should avoid duplicative review, e.g. the CDx analytical performance features are reviewed only by the NB and not re-reviewed by the EMA/CHMP or NCA.
- The IVDR states that the NB will seek an opinion from the medicinal product authority on the basis of the draft "summary of safety and performance" and the draft "instructions for use" for the CDx. Inclusion of any additional potentially helpful information should be strictly optional.
- There should be some flexibility on a case-by-case basis on the content of the submission especially the clinical performance. For example, no set expectation of precise statistics or analysis should be prescribed, as these depend on study design and type of information provided by the CDx.
- The documentation should focus on the conformity assessment aspects of the CDx without any specific HTA/reimbursement considerations. These latter aspects are outside the scope of the IVDR.

Timing:

- The timing of submissions for CDx CE-marking and medicine Marketing Authorization Applications (MAAs) should be clarified, particularly for parallel assessments.
- The timeline given in the IVDR indicates that the medicinal product authority shall deliver an opinion within 60 days of receipt of all the necessary documentation and this period may be extended once for an additional 60 days on justified grounds (see question 5)
- The co-review pathways must be closely co-ordinated by EMA/NCAs and NBs so that there is no delay for medicinal products that make use of an accelerated pathway.
- The co-review should not adversely impact the assessment review and approval of either the medicine or the CDx or delay patient access.

Participants:

- Where appropriate, the medicinal product applicant and the CDx applicant need to be involved in interactions between the Medicinal Product Authority and NB.

Engagement and co-ordination by medicines authorities, NBs and applicants will be key to ensure a workable and flexible pathway. It is also important that the interaction between the medicines authorities and NBs is co-ordinated across Member States to ensure harmonisation and rapid access of innovative medicines and CDx tests to patients.

A roadmap of when procedural guidance/Q&A can be expected would be helpful.

EFPIA/MedTech Europe Request

EFPIA/MedTech Europe would like to propose that:

(1) Information is added to the EMA Q&A and the CAMD FAQ Q&A on implementation of the MDR and IVDR to outline the pathway for the EMA/NCAs and NB co-review process, including details of the roles and responsibilities, the processes for interaction between EMA/NCAs and NBs, ***general guidelines for the scope of content and focus of review***, as well as timing of the various assessments (i.e. define the "how and when to interact/align")

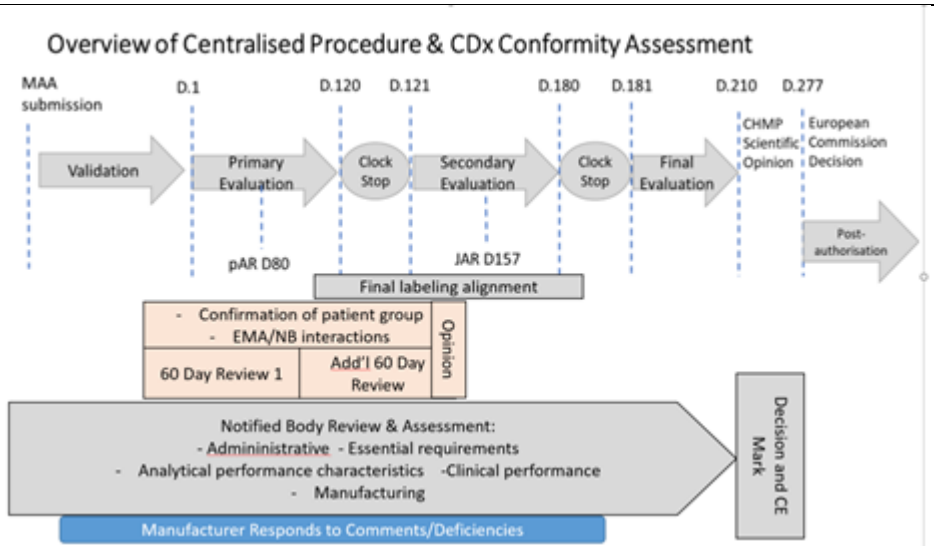
(2) The Q&A document should outline how a future CDx for a medicinal product (follow-on diagnostics), addition of a new medicinal product, or adding a new indication to an existing CDx could be enabled to drive clinical practice, as it is acknowledged that the

	one medicinal product-one test paradigm is not sustainable. A guidance on the process/level of information required/timelines for extension of the scope of a CDx for addition of a new medicinal product should also be made available. Consideration should also be given to activities that may be required in the post-licencing phase. (3) Generation of a roadmap outlining when Q&A documents and/or future guidance will be available relating to CDx under IVDR. (4) Consideration should be given to a pilot process to pressure test the overall co-review process. EFPIA/MedTech Europe would be willing to support such an endeavour should it be agreed. Following the pilot, publication of a more formal guidance by MDCG could be considered.

3	**How will differences of opinion during review be resolved?**
	<u>Background</u> As CDx are classified as Class C, there will be a mandatory involvement of a Notified Body in the conformity assessment process. In addition, the associated medicinal product will be reviewed by the appropriate medicinal product authority, either the EMA or a National Competent Authority and the same authority will be consulted during review of the CDx. EMA/NCA will systematically review the Summary of Safety and Performance of the CDx with an assessment period of 60 days. This 60-day period may be extended only once, on scientifically valid grounds. Under this procedure, the NB must give due consideration to the opinion expressed by the EMA/NCA. However, it is unclear, as yet, what would happen in the case of disagreements between NB and EMA/NCAs. Further issues may arise during non-standard reviews. This topic is addressed in Question 5. <u>Position Statement</u> Technically, according to the IVDR, the approval of a CDx by the NB requires that EMA/NCA input be obtained and considered. The procedural guidance of the co-review process should include a defined mechanism for resolution of conflict in case of issues arising between NBs and EMA/NCA. This resolution process would need to include other parties, such as the CDx manufacturer's competent authority, for a decision. Resolution of issues would need to occur within the 60 day + additional 60-day timeline given in the IVDR. The medicines and CDx applicants should be included to resolve questions and/or consider options where appropriate. A pilot activity could be run to pressure test the process and understand if there are any gaps. <u>EFPIA/MedTech Europe Request</u> EFPIA/MedTech Europe would like to propose that: (1) Clarification regarding a conflict resolution process should be provided. (2) Consideration should be given to a pilot process to pressure test the co-review process. EFPIA and MedTech Europe could provide support to develop this pilot project.

4	**What analytical and clinical performance requirements will be essential to fulfil the marketing authorization for the medicinal product and the CE mark requirements for the companion diagnostic?**
	Background To be placed on the market in the EU, a CDx must fulfil the conformity requirements as laid out in the IVDR. This is a regulatory requirement for the CDx, the CE marking requirement originates from the IVDR and is not mentioned in Directive 2001/83/EC. To meet the general safety & performance requirements in Annex I of IVDR, CDx manufacturers must follow the procedures set out in Annex IX or X combined with XI. General conformity assessment procedures for the CDx as outlined in Article 48 include Annexes IX to XI. For CDx, the notified body shall consult a competent authority designated by the member states in accordance with Directive 2001/83/EC of the European Parliament and of the Council (1) or the EMA, as applicable. Certain deliverables for IVDs (incl. CDx) are defined in Annex XIII, Part A: Performance Evaluation Report, which shall include, among other items: the scientific validity report, the analytical performance report, the clinical performance report and an assessment of those reports allowing demonstration of the clinical evidence. Analytical performance expectations are well-defined using typical parameters for IVDs. Scientific validity requirements can be fulfilled by describing the association between the biomarker measured by the CDx and the medicinal product's mechanism of action in the particular pathological state of the patient. Position Statement Clinical evidence requirements include the need to describe the clinical performance of the CDx in the context of the medicinal product performance and outcome. We believe this can be achieved in several ways: • Directly, by including the CDx in the pivotal medicinal product study. • Indirectly, via a bridging study by remeasuring trial samples with the final CDx, or even less directly by comparing the performance of the final CDx and the assay used in the trial and using appropriate statistical methods to impute the clinical performance of the target medicinal product in the population defined by the CDx. This approach works well with follow-on CDx, as explained further in Question 9. In the future, we anticipate that, subject to assurance of relevance and reliability, real-world evidence (e.g. data generated in other jurisdictions) may be used to generate clinical evidence for additional CDx/medicinal product claims. EFPIA/MedTech Europe Request EFPIA/MedTech Europe request guidance specifying which CDx performance characteristics are to be reviewed exclusively by the NB and which (such as the clinical evidence) should be included in the joint assessment. This will allow review redundancies to be avoided. The guidance should also describe alternative ways of generating the necessary clinical evidence for CDx.

5	**What will the timelines for a standard co-review be?**
	Background A schematic was presented at the EMA multi-stakeholder workshop on 'predictive biomarker-based assay development in the context of medicinal product development and lifecycle' on 18th June 2018 demonstrating the separate timelines for the CDx consultation process and the review and approval process for a medicine in the centralised procedure. The proposed timelines may not, however, be optimal, particularly if the CHMP review of the NB opinion extends into 120 days as this could delay the medicine review. Furthermore, the timeline for the NB review process also needs to be considered. Position Statement A detailed overview of aligned timelines for the review of the CDx submission needs to be generated to bring Regulators in Europe, including the European Medicines Agency, NCA, Notified Bodies and industry to a common understanding. The proposed schematic below shows the timeline for the (a) NB/ EMA-NCA CDx consultation process, (b) the centralised procedure process for the associated medicine review and (c) the process for NB review of the CDx. Proposed assumptions and interactions among the timelines are included. If we assume a clock stop will be needed after the primary evaluation of the medicinal product, the outcome of the CHMP review of CDx documentation is required by the end of the primary evaluation (D120) of the medicine, as the applicant(s) need to understand early in the process if there are questions/issues relating to the CDx. If there is an additional 60-day period required to get to a final CHMP opinion, this could be continued in parallel to the clock stop period/secondary evaluation phase of the medicine. The final opinion for the CDx would need to be agreed before Day 180 of the standard timeline in the centralised procedure in case there is no list of outstanding issues (LoOI). From the point of view of the CDx assessment, the consultation with EMA/NCA can begin as early as possible after submission to the NB and for efficiency's sake could occur in parallel with other elements of the NB review and assessment of conformity with the essential principles of IVD performance. During the 60 + 60-day period interactions between NB, EMA-NCA, the manufacturer of the test and the medicinal product sponsor can take place during the EMA/NCA consultation if necessary, e.g. if different data analyses/populations are requested, etc. Additional interactions between NB, EMA/NCA, the manufacturer of the test and the medicinal product sponsor should be considered in order to align information appearing in the final labelling of the CDx and the medicinal product and to align on any post-licensing requirements.



Assumptions:

1. The timelines above are for a **standard review**
2. If CDx conformity assessment file contains clinical information from the same clinical trial as the medicine, CDx and MAA will be submitted to the NB and EMA respectively in parallel
3. CDx documentation is ready to submit to EMA during the NB review
4. If EMA (CHMP) agrees with CDx documentation (i.e. SSPE, IFU etc), EMA (CHMP) opinion issued within 60 days
5. If EMA (CHMP) disagrees with CDx documentation (i.e. SSPE, IFU etc), EMA (CHMP) opinion issued within 120 days
6. The EMA (CHMP) assessment of the CDx documentation can be done in parallel with the medicine assessment but does not stop at medicine clock stops
7. The consultation with EMA/NCA can begin as early as possible in the NB review of the CDx and can take place in parallel to other aspects of the CDx conformity assessment.

<u>EFPIA/MedTech Europe Request</u>

EFPIA/MedTech Europe would like to propose that:

1. A detailed timeline for the review of the CDx submission needs to be provided (including detailed timelines for decentralised and mutual recognition procedures).
2. The proposed timeframe should stipulate that the outcome of the CHMP review of CDx documentation is required by the end of the primary evaluation (D120) of the medicine. If there is an additional 60-day period required to get to a final CHMP opinion, this could be continued in parallel to the clockstop period/secondary evaluation phase of the medicine.
3. The proposed timeframe should stipulate that the final opinion for the CDx would need to be agreed before Day 180 of the standard timeline in the centralised procedure in the case that there is no list of outstanding issues (LoOI).
4. From the point of view of the CDx assessment, the consultation with NB, EMA/NCA, the manufacturer of the test and the medicinal product sponsor can begin as early as possible following submission to the NB and for the sake of efficiency should occur in parallel with elements of the NB assessment of conformity with the essential principles of IVD performance.
5. Interactions between NB, EMA-NCA, the manufacturer of the test and the medicinal product sponsor could occur during the 60 - (or 120-) day consultation process (e.g. if different data analyses/populations are requested, etc).
6. Additional interactions between NB, EMA/NCA, the manufacturer of the test and the medicinal product sponsor should be considered in order to align information appearing in the final labelling of the CDx and the medicinal product.

6	**In a situation where the medicinal product is in an accelerated procedure (e.g. conditional approval) how will approval of the companion diagnostic be handled? Will accelerated review of the CDx be initiated?**
	Background The pharmaceutical legislation has several provisions to enable accelerated approval and earlier access to innovative medicinal products for patients (e.g. accelerated assessment, PRIME scheme, conditional marketing authorisation, adaptive pathways, Early Access Programs). The IVDR, on the other hand, contains no such provisions. This situation could lead to a lack of coordination and potential delays in the companion diagnostic test registration for medicinal products that make use of an accelerated regulatory pathway. Position Statement Patients' ability to access a promising new targeted treatment for an unmet medical need must not be slowed down due to the absence of an accelerated approval process for the associated companion diagnostic. The availability of a CDx to guide the new treatment serves to improve outcomes for patients. An ideal solution would be to create a formal registration pathway for 'breakthrough' medical devices and IVDs, but such an endeavour may be beyond the bandwidth of stakeholders who are currently fully occupied with basic implementation of the MDR and IVDR. Instead, the EMA/NCA and NB interactive process, that is currently being built by the relevant stakeholders, must be flexible enough to allow for acceleration in cases where it is warranted. Features of successful 'breakthrough device' programs (reference US, China, Japan) should be replicated to the extent possible in the interactive implementation pathway currently being built. These include the following: • **Eligibility criteria**: Because CDx are essential to the safe and effective use of their corresponding medicinal product, any CDx associated with a medicinal product in an accelerated approval process should be automatically eligible for acceleration considerations. • **Early and frequent interaction with reviewers**: The value of early dialogue involving all stakeholders (medicinal product and diagnostic manufacturers, EMA/NCA and NB) has been previously discussed. Additional considerations available in an accelerated program might include: appointment of a single point of contact, involvement of more senior health authority officials and commitment to well-documented feedback and interactions with shorter timelines than typically experienced. A more flexible model for queries and advice, less formal and lengthy than the formal Scientific Advice process, should be developed. • **Clinical study and development advice**: The goal of early multi-stakeholder interaction, as noted above, is to arrive at a cohesive and comprehensive clinical development plan. In a 'breakthrough' or accelerated program, health authorities should be prepared to consider and advise on novel study designs (e.g. umbrella trials, basket trials, adaptive trials). • **Shift of focus from pre-market to post-market data collection**: The IVDR includes provision for a mechanism to support "Post-Market Performance Follow Up (PMPF)" prior to issuance of a CE-certificate. For an accelerated medicinal product and diagnostic pair, health authorities should consider whether assurance of post-market surveillance/related data collection studies could adequately lower the risk profile and enable a favourable decision. For example, the US Breakthrough Program asks reviewers to formally consider whether it may be appropriate to shift some data

	collection activities to the post-market setting. Advances in real-world data generation, aggregation and analysis may further facilitate collection of post-market data and such evidence should be considered for regulatory decision-making subject to assurances of relevance and reliability to enable accelerated review if appropriate. • **Priority registrational review**: For programs where the review timelines for the medicinal product are formally shortened, the CDx registration process should be voluntarily accelerated as well. Though statutory timelines may remain unchanged, a principle of "top-of-queue review" could be imposed by the Notified Body. For those parts of the review involving interaction between EMA/NCA and the NB, the timeline expectations should be proportionally reduced to meet the accelerated medicinal product timelines. The above features, which appear in existing successful breakthrough device programs (such as e.g. in the US, China and Japan), could be leveraged as intentional options during the development and subsequent review of a targeted medicinal product and its associated CDx. Such additional effort is vital to ensure that the most promising innovative therapies and diagnostics can reach the patients who need them in a timely manner. <u>EFPIA/MedTech Europe Request</u> EFPIA/MedTech Europe would like to propose that EMA/NCA and NB adopt a flexible interactive approach to medicinal product/companion diagnostic review to allow for acceleration in cases where it is warranted. Such flexibility should take into account (i) automatic eligibility for acceleration for CDx where warranted, (ii) early and frequent access with reviewers, (iii) access to rapid clinical study and development advice, (iv) support for obtaining data in the post-market rather than premarket setting and (v) priority registrational review.

7	**If acceleration of the CDx approval is not possible, can the medicinal product be approved ahead of the CDx?**
	<u>Background</u> Because companion diagnostics are, by definition, essential to the safe and effective use of their corresponding medicinal product, a targeted medicinal product should not be approved or placed on the market without an approved companion diagnostic. Exceptions can be made in the case of high unmet medical need. <u>Position Statement</u> If a medicinal product meets the criteria for PRIME designation and achieves conditional approval, then the development and CE-marking of the associated CDx could, under exceptional circumstances, be made a post-approval commitment for the medicinal product. Since the patients will still need access to testing in the interim, some arrangements should be made for them to have access to the testing that was used in the medicinal product clinical trial or another acceptable alternative (e.g. send out tests to a jurisdiction where the test is approved).

	EFPIA/MedTech Europe Request EFPIA/MedTech Europe would like to propose that in circumstances where accelerated or conditional approval of a medicinal product is achieved but where the companion diagnostic is not in a position to achieve simultaneous approval, the medicinal product is approved with a post-approval commitment for the approval of the CDx. In addition, appropriate transitional arrangements for testing of appropriate quality (e.g. use of defined clinical trial assay) should be agreed to ensure patients can access the therapeutic upon its approval.

8	**How will the labelling of the medicinal product and CDx be co-ordinated? What information will be included in the label of the medicinal product and in the label of the CDx? In which sections of the label will the information reside?**
	Background For the first time, the IVDR introduces new requirements for a formal assessment by a medicinal products authority of the suitability of a CDx for a medicinal product. This pre-market assessment is carried out upon request by the Notified Body, which is certifying the CDx and is provided in the form of a scientific opinion by either the European Medicines Agency or a national medicinal products authority. Post-market, whichever body provided the scientific opinion is kept informed of any serious incidents with the companion diagnostic. While the IVDR has requirements for information which accompanies the companion diagnostic regarding the medicinal product for which it makes a formal claim, the medicinal products legislation has no specific requirements about how to provide information about the companion diagnostic on the medicinal product label. In particular, the medicinal products legislation does not differentiate between a predictive biomarker test and a CE-marked companion diagnostic. As the IVDR now requires that the test be CE-marked on the basis that it is '*essential for the safe and effective use of the corresponding medicinal product*…', it makes sense for the medicinal product label to specifically identify where a predictive biomarker test is a CDx. To ensure transparency of information about these diagnostic tests, the European Commission should provide a comprehensive list of all CDx via the Eudamed medical devices database. ***Information accompanying the CDx and the medicinal product*** *1. Information accompanying the CDx* The CDx label must contain the details strictly necessary for the user to identify the medicinal product and, where it is not obvious for the user, the intended purpose of the device. The CDx instructions for use must contain: • Intended purpose and function as a companion diagnostic • The international naming nomenclature (INN) of the corresponding medicinal product • Identification of a website where the device summary of safety and performance is made available to the public via Eudamed

Therefore, the CDx label and accompanying information must specifically identify the medicinal product for which it is a companion diagnostic. It also provides transparent information to the public about the CDx via a summary of safety and performance.

2. Information accompanying the medicinal product
According to the European Union SmPC guideline section 4.1, Therapeutic Indications: "If the product's indication depends on a particular genotype or the expression of a gene or a particular phenotype, this should be stated in the indication." Today, medicinal product labels for the European market state the predictive biomarker test, where relevant, in the indication. The label does not specify if the test is a companion diagnostic. In fact, it is only when predictive biomarker tests are CE-marked as companion diagnostics under the IVDR that making a distinction between a general predictive biomarker assay and a companion diagnostic becomes possible.

European Union SmPC guideline section 5.1, Clinical Particulars, provides a summary of clinical trial information. Sometimes the predictive biomarker which was used and its brand name and or manufacturer are mentioned here.

EMA should mandate that the medicinal product labelling must specify the use of an approved test if there is a companion diagnostic indicated for that product.

<u>Position Statement</u>
From a regulatory standpoint, it is important that the need for a CDx test should be described and appropriate that the label of the medicinal product should specify the use of a corresponding CDx which is compliant to the IVDR. The CDx is CE-marked under the claim that it is essential for the safe and effective use of the corresponding medicinal product to identify patients who are more likely to benefit or suffer increased adverse effects from treatment with the medicinal product. For prescription clarity and hence safe use of the medicinal product, it is important that the need for an IVDR-compliant companion diagnostic test should be reflected in the labeling.

In the United States, the Food and Drug Administration (FDA) mandates that the medicinal product labelling must specify the use of an FDA-approved test if there is a companion diagnostic indicated for that product. It would be appropriate to take a similar approach in the European Union.

Also, FDA publishes a list of approved CDx and their corresponding therapeutic products that is publicly available. To ensure transparency of information the European Commission should provide a comprehensive list of all companion diagnostics via the Eudamed medical devices database in a similar manner to the approach taken by the FDA.

<u>EFPIA/MedTech Europe Request</u>
EFPIA and MedTech Europe therefore propose that:

- **Therapeutic Indications section 4.1 of the SmPC guideline should be updated** to require mention of a companion diagnostic for the medicinal product which is compliant with the IVDR whenever a CDx is needed.
    - There should be flexibility for the medicinal product manufacturer to craft the wording of the indication. Possible wording could be e.g., "...for treatment of patients with biomarker XYZ as confirmed by a CDx test which is compliant with the European Union IVDR."

- Medicinal product labelling should allow the marketing authorization holder to **optionally** include use of the companion diagnostic brand name (e.g. as an example of available testing) and at the same time avoid limiting use of any other current or future companion diagnostic that is IVDR-compliant for the named medicinal product.
- Different language may be necessary in the case of conditional approval that may happen before a CE-marked CDx is on the market.

- **Clinical Particulars section 5.1 of the SmPC guideline should be updated to note specific identification information (e.g. brand name and/or manufacturer)** of the original companion diagnostic.
  - Such mention may be case-specific, i.e. driven by how much detail is required to interpret clinical trial results and context.
  - There should be no need to update existing labels if the brand name and manufacturer currently are not mentioned under section 5.1.

- **A list of companion diagnostics which have been CE-marked under the IVD Regulation should be made available to the public via the Eudamed medical devices database.**
  - Eudamed will have the capability to identify IVDs which are registered companion diagnostics, because this is a required data field.
  - Eudamed should provide a comprehensive list of all companion diagnostics (including in-house companion diagnostics). This will help physicians, laboratories and the general public to identify these devices and search Eudamed to find information about the companion diagnostics, i.e. via their summaries of safety and performance.

It is important to find a consistent approach to identifying the companion diagnostic or medicinal product labelling which ensures prescription clarity and hence safe use of the medicinal product. It is equally important to provide transparency of information on companion diagnostics which are available in Europe. An up-to-date list of companion diagnostics should also be made available on the Eudamed public website.

<u>EFPIA/MedTech Europe Request</u>
EFPIA/MedTech Europe would like to propose that medicinal product labelling should reflect use of CDx which are compliant with the IVD Regulation.

These proposals are:
- Therapeutic Indications section 4.1 of the SmPC guideline should be updated to require mention of a companion diagnostic for the medicinal product which is compliant with the IVDR whenever a CDx is needed.
- Clinical Particulars section 5.1 of the SmPC guideline should be updated to note the specific identification information (e.g. optional brand name and/or manufacturer) of the original CDx.
- A list of CDxs which are compliant to the IVD Regulation should be made available to the public via Eudamed

9	**How would review & approval of a follow-on diagnostic be conducted? What analytical & clinical performance requirements will be required to fulfil the CE Mark requirements?**
	Background A follow-on CDx is intended to be used with the medicinal product in the indicated patient population, as mentioned in the labelling of the original approved companion diagnostic. As such, the information provided by a follow-on CDx must demonstrate the ability to detect the equivalent population to the originally approved CDx to ensure the safe and effective use of the corresponding medicinal product. However, the manufacturer of a follow-on CDx may not have a therapeutic partner to conduct a new clinical trial with, or there may be a lack of patient samples from the original clinical trial, where the comparator device and medicinal product were originally evaluated. In such cases, a concordance study may be conducted to assess the agreement/similarity between the originally approved CDx and the follow-on CDx; including an appropriate statistical analysis to express the clinical performance of the follow-on CDx in terms of its corresponding medicinal product (for example, treatment outcome in CDx-selected group). Position Statement Follow-on companion diagnostic tests are new CDx tests for use with existing product already on the EU Market. The medicine was originally approved with a different CE -marked CDx test, typically the one used during the pivotal prospective clinical trial for the precision medicine. To CE mark the follow-on CDx test, it should be necessary to demonstrate comparable analytical and clinical performance with the original CDx test. Clinical validation for a follow-on CDx test could involve a performance evaluation study comparing the results of the original CE-marked CDx test with that of the follow-on CDx test by retesting the original clinical trial specimens or by obtaining specimens representative of the same intended use population. Clinical validation of a follow-on CDx test should not necessarily require use within another prospective therapeutic clinical trial with the medicinal product. Follow-on CDx clinical validity should be supported by statistical methodology such as that described in Meijuan Li (2016) *Statistical Methods for Clinical Validation of Follow-On Companion Diagnostic Devices via an External Concordance Study, Statistics in Biopharmaceutical Research, 8:3, 355-363, DOI: 10.1080/19466315.2016.1202859.* EFPIA/MedTech Europe Request EFPIA/MedTech Europe would like to propose that a specific guidance is developed to outline the key principles upon which follow-on CDx could be brought to the market. If possible, this guidance should outline scenarios or approaches for clinical validation that do not require use of the follow-on CDx in a new prospective clinical trial with the therapeutic.

10	**How will existing medicinal product/companion diagnostics products be reviewed and re-registered under IVDR?**
	Background Under the IVDR there will be no "grandfathering" of existing IVDs to the market. Therefore, all IVDs currently on the market, including diagnostics used to select patients for treatment (hereafter referred to as CDx although it is appreciated that CDx were not formally defined under IVDD) will be required to be certified under the IVDR if they are to remain on the market beyond May 2022. To date, all diagnostics currently used to select patients for treatment (i.e. CDx) in the EU have been marketed as self-certified products under IVDD. It is imaginable that devices have entered the market without external scrutiny of specific clinical validity data in support of the CDx claim. Currently there is concern among both medicinal product and IVD manufacturers that there will be insufficient provision of Notified Bodies (NBs) designated under the IVDR to conduct the required reviews of IVDs requiring (re-)assessment, including CDx. Industry concerns are threefold: 1. The additional expertise and capacity that NBs need to invest in order to sufficiently address the new requirements of the IVDR Regulation, including CDx; 2. The time and capacity needed at authority level to designate new and existing notified bodies under the Regulation; and 3. The time and capacity needed for notified bodies to complete all necessary certifications of: • products having notified body oversight for the first time, e.g. most IVDs; • products already on the market today needing re-certification to the new regulation; • new and innovative products in the pipeline to be certified for the first time The IVD regulatory framework is fundamentally changing. Not only will more IVDs be in the scope of the new Regulation, but there are also many new and strengthened requirements to be met. Moreover, ~85% of all IVDs will require NB oversight for the first time. The designation of NBs under the IVD Regulation must happen simultaneously to the designation of notified bodies under the MD Regulation and should not be postponed due to the IVD Regulation's later date of application. There are at least 40,000 IVDs on the market, of which approximately 34,000 will need oversight by notified bodies [2012 Commission impact assessment for the IVD Regulation and MedTech Europe November 2017 Position: Implementing the new IVD and Medical Devices Regulations - Early availability & capacity of notified bodies]. Assuming that 21 notified bodies will apply for designation under the IVD Regulation, each NB would, on average, need to assess at least 1,600 IVDs. To date, there has been no indication nor assurances that such capacity can be supported by the NBs proposing to undertake this activity. More troubling, as of May 2020 only 3 NB have been designated under IVDR. Moreover, recent intelligence gathered indicates that not all of the 21 NBs available under the IVDD have applied to be notified under the new rules (European Commission, Notified Bodies). The situation is especially urgent for a majority of IVDs, including companion diagnostics, that will require NB review for the first time under the IVDR, as these diagnostics would not qualify for any potential additional two-year transition because they have no NB-issued CE certificates.

In that regard, both the medical device and pharmaceutical industry urgently calls on the European Commission and the Member States to ensure the availability of notified bodies designated under the Regulation 2017/746 on *in vitro* diagnostic medical devices (IVDR) early in the transition period. A fully functioning notified body system, with sufficient capacity to manage the workload under the current and future regulatory framework in a timely manner, is vital in ensuring that patients, hospitals, laboratories and healthcare systems have continued access to safe and innovative medical technologies. Equally sufficient staff and expertise should be available within regulatory authorities of the pharmaceutical sector, e.g. European Medicines Agency, National Competent Authority etc.

It is also unclear what data will be required to support the application of an existing CDx to ensure its certification under IVDR. Under the IVDR, new companion diagnostics, in addition to meeting the general safety & performance requirements in Annex I of the regulation, must follow the general conformity assessment procedures as outlined in Article 48, which include conformity assessment as outlined in Annexes IX to XI. Certain deliverables for IVDs (including CDx) are defined in Annex XIII, Part A. A Performance Evaluation Report, which shall include: the scientific validity report, the analytical performance report, the clinical performance report and an assessment of those reports allowing demonstration of the clinical evidence is required. Summarily, under the IVDR, manufacturers are required to have on file a performance evaluation report that includes scientific validity data, analytical performance data and clinical performance data, as applicable, based on the product's intended use. For many diagnostics currently used to select patients for treatment on the market today, identifying, compiling and/or generating clinical performance data may prove challenging, as these devices were not used for the original pivotal clinical trials and samples from the pivotal trials may no longer be available (or accessible to the diagnostic manufacturer).

For companion diagnostics, it is also stipulated that the notified body shall consult a competent authority designated by the Member States or the EMA, as applicable. As such, a procedure is required; this will add significantly to the workloads and timelines, further increasing risk to patients.

Overall, this situation poses serious threats to the continuous supply of life-changing precision medicines currently on the market, many of which are supported by the market availability of diagnostic products currently used to select patients for treatment that have been used safely for years. Thus, it is critical that there is continuity of CDx availability for already approved medicinal products to ensure that patients can access essential, approved, life-changing therapeutics.

<u>Position Statement</u>
To maintain continuity of supply of critical diagnostics currently used to select patients (i.e. CDx) for already approved medicinal products on the market, the EMA/NCA and NB must provide an infrastructure for rapid, expedient review of applications. Early, clear guidance is required to openly lay out the required expectations. This guidance should specifically address (i) the procedure required for the evaluation and re-certification of current companion diagnostics, (ii) the timelines for review and (iii) the expectations for performance evaluation documentation. Most importantly, this guidance should also address the acceptable alternate mechanisms for the provision of clinical performance data for cases where there are no means of accessing such data from the pivotal trials (or residual samples from such pivotal trials). Such approaches could include the use of alternative data sources such as data submitted in support of companion diagnostic registrations in jurisdictions already requiring review of clinical

	evidence (e.g. US or Japan), concordance data to CDx approved in those jurisdictions (supported by appropriate statistical analysis to express CDx performance in terms of the medicinal product performance), or use of real-world evidence (specifically marketing experience) in support of therapeutic claims subject to assurances of relevance and reliability, etc. EMA/NCA and NB must also work to establish a priority review process to allow expeditious review of already approved CDx currently available on the market for corresponding medicinal products, to enable treatment with potentially lifesaving therapeutics. Designation of sufficient NBs, skilled in the review and assessment of companion diagnostics, is critical. Assurances must also be made to ensure the provision of sufficient, skilled staff to ensure volumes and timelines can be met. Development of programs and/or facilities to train and educate staff at NBs in the assessment and review of companion diagnostics is also pivotal. Given the potential challenges for re-certification of diagnostics currently used to select patients for treatment, EMA/NCA and NB should identify alternative testing arrangements that should be considered in order to ensure continuity of testing to aid therapeutic decision-making in the event that current diagnostics used to select patients for treatment cannot be re-certified in a timely manner. <u>EFPIA/MedTech Europe Request</u> EFPIA/MedTech Europe would like to propose: 1. Publication of guidance describing how re-certification of already existing diagnostics currently used to select patients for treatment will be conducted is required. This should include (i) the procedure required for the re-certification and evaluation, (ii) the timelines for such review and (iii) the expectations for performance evaluation documentation. 2. Guidance should also be developed to outline how clinical performance data may be identified and delivered in situations where there is no access to data or samples from the original pivotal clinical trial. 3. EMA/NCA and Notified Bodies should establish a procedure for priority review of companion diagnostics seeking re-certification under IVDR. 4. Mechanisms to facilitate provision of sufficient NBs, with appropriately trained and skilled personnel, should be put in place to deliver the review and re-certification of companion diagnostics in a timely manner. 5. Should there be delays to the re-certification process for a companion diagnostic which jeopardises access to a precision medicine, alternative testing arrangements should be considered in order to ensure continuity of testing to aid therapeutic decision-making.