



The Royal College of **Pathologists**

Pathology: the science behind the cure

Response from the Royal College of Pathologists to consultation on the MHRA guidance on companion diagnostic IVDs

The Royal College of Pathologists' written submission

July 2016

For more information please contact:
Rachael Liebmann
Registrar

The Royal College of Pathologists
4th Floor
21 Prescott Street
London
E1 8BB

Phone: 020 7451 6700
Email: registrar@rcpath.org
Website: www.rcpath



1 About the Royal College of Pathologists

1.1 The Royal College of Pathologists (RCPATH) is a professional membership organisation with charitable status. It is committed to setting and maintaining professional standards and to promoting excellence in the teaching and practice of pathology. Pathology is the science at the heart of modern medicine and is involved in 70 per cent of all diagnoses made within the National Health Service. The College aims to advance the science and practice of pathology, to provide public education, to promote research in pathology and to disseminate the results. We have over 10,000 members across 19 specialties working in hospital laboratories, universities and industry worldwide to diagnose, treat and prevent illness.

1.2 The Royal College of Pathologists response reflects the position of the Royal College of Pathologists formulated by Professor Ian A Cree, Research Committee chair, with input from Prof Tim Helliwell, V-P for Learning.

2 CONTENTS

2.1 The Royal College of Pathologists welcomes the draft document which it considers to be generally very helpful and pragmatic. The comments and suggestions below are intended to make improvements for the benefits of patients and to allow greater utility of the guidance.

2.2 The comment has been made that the statement that IVDs are currently regulated under EU Directive 98/79/EC may need to be updated given the recent UK referendum decision to leave the EU.

2.3 In the draft Definition section it states that for the purposes of this guidance, MHRA have defined a companion diagnostic IVD as an IVD that is intended by the IVD manufacturer as essential for the safe use of a corresponding medicinal product. This is considered by the College to be an issue. For instance EGFR testing is essential to guide the use of EGFR inhibitors in lung cancer, but multiple manufacturers offer tests – so which one is essential? The RCPATH would recommend removal of the role of the manufacturer in determining this, as, in the example used, the IVD is actually defined in the approval document for the drug(s) active against EGFR. In addition, the College considers the definitions of "essential" and non-essential diagnostics on page 4 are not tight enough. If essential has to be defined by the manufacturer, then there is a risk that manufacturers will try to make companion IVDs "desirable" rather than essential to avoid some of the associated regulation.

2.4 The examples given of Imatinib (Gleevec) and Cetuximab (Erbix) illustrate the above point since tests for both are essential for safe use of the drug, but are not defined by the IVD manufacturer. In the opinion of the RCPATH the FDA definition, 'An **IVD companion diagnostic** device is an **in vitro diagnostic** device that provides information that is essential for the safe and effective use of a corresponding therapeutic product' is better.

2.5 In the subsequent section on page 5 which introduces companion diagnostics, and also elsewhere in the document, the College would recommend underlining the phrase companion diagnostics to emphasise when the document is talking specifically about Companion Diagnostic IVDs.

2.6 Regarding the statement in the section titled Product development that ‘discovery would be followed by the analytical validation of the proposed companion diagnostic test, followed by clinical validation and leading on to the development of the stratified medicine’ the comment has been made that in practice this usually occurs the other way around.

2.7 An issue was raised with the statement in the section on Regulation of tests used in medicinal product development and clinical trials ‘If the diagnostic device is used as an exploratory tool within the trial but not for patient allocation or randomisation eg results of the diagnostic are not used or not available during the trial then the IVD will EITHER need to be CE marked OR registered with the devices regulator as a device for performance evaluation.’ Specifically, a drug trial may be performed with a RUO test that proves very efficacious and/or effective. It would be unethical to repeat the trial and the RUO product would be validated within the trial fortuitously. It would then need registration, but if this had not been done there would be no way to repeat the trial and no way to obtain Companion Diagnostic IVD approval. The College would recommend including RUO in this paragraph with later registration: the IVD is not being used for patient allocation and so this is considered to be safe.

2.8 Regarding the draft section on Medicinal product clinical trial design models the statement ‘The possible designs and their potential applications are pictorially represented below’ the comment was made that the diagrams are helpful and fairly comprehensive but the College would recommend inclusion of the adaptive trial design.

2.9 In the Product information section the statement is made that ‘The medicinal product information (SmPC, investigator’s brochure and/or protocol) should include reference to the companion diagnostic IVD, particularly in the pivotal clinical trials. Medicinal product information should set out the intended use and performance characteristics of the companion diagnostic IVD.’ However the RCPATH would comment that this can result in issues. PDL1 testing using a particular antibody is mandatory for the use of PD1 inhibitors, but only some labs have the particular manufacturer’s equipment. The result is a lack of testing and reduced competition between manufacturers, which could prevent another manufacturer with a better test entering the market. The College would suggest the phrase, ‘Medicinal product information should set out the intended use and performance characteristics of the companion diagnostic IVD(s) applicable.’

2.10 Similarly an issue is identified with the draft question: ‘However, under the current legislations, specific direct mandated use of the device prior to use of the medicinal product is not anticipated/recommended/permitted?’ The RCPATH considers this to be an issue and suggests significant re-wording as the point of a companion diagnostic is that it is used before the medicinal product is prescribed.

2.11 Regarding the draft section on Guidance on CE marking of IVDs: ‘For an IVD, the CE mark represents the manufacture’s declaration that the product meets all of the essential requirements of the IVD Directive. This includes requirements for safety, quality and performance. It does not include requirements for clinical utility or other health economic indicators.’ The College points out that these factors are taken into account in NICE DAP assessments.

2.12 The diagram on Page 11 applies to new drugs and companion diagnostics, but would recommend that another diagram is needed for existing drugs with or without existing companion diagnostics.

2.13 In the section on Matching the test with the drug - Working together it is stated that ‘MHRA assume that the manufacturer of the medicinal product and the in vitro diagnostic medical device should have appropriate contracts and lines of communication in place. This is especially important during co-development.’ The RCPATH would point out that this will not apply to third party companion diagnostics, which may exceed the performance of the initial one and even use a new technology (e.g. RNA instead of protein measurement). Also on this page in the section on the Intended purpose of the test - the College would recommend that the authors consider guidance on dual purpose testing - e.g. testing for a marker which gives both diagnosis and stratification for trials. Clarity in this document on dual purpose testing would be helpful.

2.14 Regarding the section on Laboratory accreditation and quality assurance it is stated that ‘The laboratory should be able to demonstrate its ability to carry out this testing by using accreditation to ISO 17025 (*General requirements for the competence of testing and calibration laboratories*) or ISO 15189 (*Medical laboratories — Particular requirements for quality and competence*).’ The RCPATH is not sure about the reference to ISO17025 here. Although this is appropriate for EQA schemes, all molecular pathology labs should have ISO15189 in the UK and would refer the authors to the RCPATH/ESP guidance for Molecular Pathology.

2.15 In the section on Concordance reference is made to ‘the SPC assay’ and we would suggest that this abbreviation is clarified on first use.

2.16 The section on Future legislation on page 15 will need to be amended to take into account the position vis a vis the EU following the 2016 referendum.

2.17 The RCPATH welcomes the inclusion of links to relevant information and guidance and looks forward to seeing these included within the final document.