MHRA Guidance on companion diagnostic IVDs – CRUK response

Cancer Research UK anticipates that the use of molecular diagnostic testing will play a key role in the future of cancer clinical trials and access to precision medicine, and we welcome the opportunity to respond to this consultation. We spend £30-40m per year directly on precision medicine, supporting 11 large stratified trials as well as funding other large programmes and infrastructure. We are increasingly moving towards a model where cancer patient treatment decisions are made on an individual basis at the initiation of treatment, monitoring response, and at the point of recurrence.

Molecular diagnostic tests present an opportunity to radically improve our ability to tailor treatments to individuals. As more targeted therapies become available, there will be an increasing need for clinicians to routinely perform diagnostic testing and interpret complex data sets – and to do all this in a way that can benefit therapeutic choices in real-time.

Recent advances in detecting circulating tumour cells (CTCs) and circulating free DNA (cfDNA) as well as improvements in functional imaging, provide the promise for decision-making based on genetic and phenotypic aspects of the tumour, without the need for invasive procedures. Additionally, stratification of patients 'out' of treatments to which they will not respond will prevent potential harmful side effects.

The comments we have developed in response to this consultation relate predominantly to the issue of the requirement for CE registration of assays for use in clinical trials:

- The requirement to CE register an assay prior to establishment of clinical utility will place an undue regulatory burden on clinical research
    - We ask for the requirement for CE marking to be postponed until after clinical utility has been established.
- CE marking should not be the sole mechanism of external Quality Assurance
    - We ask that the guidance requires due diligence in Quality Assurance prior to establishment of clinical utility, rather than CE marking
- Panel testing is on the increase and the guidance should be future-proofed accordingly
    - We ask that CE Marking is not mandated prior to establishment of the clinical utility.
- There is a need for clarification on whether in-house exemptions apply to patients from another site
    - We would strongly support the phrasing of the existing guidance being retained in the proposed guidance

The requirement to CE register an assay prior to establishment of clinical utility will place an undue regulatory burden on clinical research

Establishing the link between a known biomarker and a potential therapeutic is a vital early step in assay development. Due to the cost, time delay and regulatory burden, it would be infeasible to apply for CE registration at such an early stage, prior to the clinical utility of that biomarker/drug being known.

In particular the cost of using CE Marked tests would make running academic biomarker-driven trials unviable in the UK. If CE Marked testing for RAS were incorporated within the FOCUS4 trial, which requires a panel testing approach, it would cost £250 per sample for NRAS and KRAS alone, as

opposed to £300 for the full panel of tests. The resource and funding implications for acquiring CE Marking for Laboratory Developed Tests (LDTs) would also significantly prohibit academic trials.

However, once clinical utility has been established, CE marking becomes an appropriate Quality Assurance step prior to establishing clinical validity of an assay.

CE Marking should not be the sole mechanism of external quality assurance

Assays can be fully validated and robust without CE Marking.

Cancer Research UK funded academic trials that are stratified by biomarker status are run in laboratories that adhere to Good Laboratory Practice (GLP). They have United Kingdom Accreditation Service (UKAS) accreditation, robust validation processes and participate in the National External Quality Assurance Scheme (NEQAS) in addition to regular sample swaps between testing labs to confirm consistency. These standards allow locally-developed tests to ensure high quality and robustness without the need for CE Marking in the clinical trial stage of testing.

In addition, some standard of care tests, as well as trial tests, are currently carried out using robust and well-validated tests that are not CE Marked.

For example, a patient suspected of having Chronic Myeloid Leukaemia (CML) will usually have a cytogenetic analysis using an LDT approach. There isn't a commercial kit specifically for chromosome analysis. Cytogenetic identification of t(9;22) by G-band analysis is considered sufficient. Confirmation may be by RT-PCR – also usually an LDT. It would cause unnecessary delay in diagnosis and treatment, and additional cost, if further confirmation using a CE marked FISH test (or alternative CE marked product) was required in addition to the other tests.

Panel testing is on the increase and the guidance should be future-proofed accordingly

We are moving away from using just one companion diagnostic (CD) and increasingly towards panel testing. Whilst a panel is still in the research phase (i.e. to stratify patients into trials testing the clinical utility of the marker/drug) it is vital that CE Marking is not mandated prior to establishment of the clinical utility.

The single companion diagnostic expectation which drives a philosophy of identifying the "right patient for the drug", will shift towards to a multiplex/comprehensive testing approach which encourages identifying the "right drug for the patient". The panel approach will identify all relevant companion diagnostics and the clinician and patient then have a choice available to them which takes into account issues such as co-morbidities.

In order to incorporate new genes/regions/aberrations into a panel, a re-design followed by a robust validation step is carried out. It is important that panels are able to be updated using a flexible yet adaptive approach, and are not restricted to using only CE marked tests.

Clarification on whether in-house exemptions apply to patients from another site

The proposed guidance appears to have shifted significantly from the August 2013 guidance, which supported in-house developed tests being used on patients from one or more NHS Trust. This was a valuable and pragmatic exemption, since it allowed us to develop centralised labs with a critical mass of expertise under the control of robust quality management systems. Labs participate in regular sample swap quality control, and participate in National EQA schemes run by NEQAS.

The proposed guidance appears to have become more restrictive in this regard – i.e. an exemption is permitted if the site tests only its own patients. Cancer Research UK understands that MHRA are seeking to clarify this issue, which we would welcome, and we hope that they will be able provide reassurance that in-house exemptions for samples from other sites will continue to apply.

We are concerned that if the exemption only applies to patients from the manufacturing trust, this may have the unintended consequence of forcing funders to abandon the concept of large multi-centre studies and only run trials in sites that have accredited labs. Alternatively each site may be required to develop their own test, which would eradicate the known benefits of centralised testing.

The existing guidance is highly robust, yet pragmatic, and we would strongly support the phrasing of this being retained in the proposed guidance:

Article 1.5 of the Directive (see Regulation 33) excludes from its scope devices 'manufactured and used only within the same health institution and on the premises of their manufacture or used on premises in the immediate vicinity without having being transferred to another legal entity.'
The MHRA's view is that the exemption above will apply where a health institution manufactures an IVD in-house and then uses that IVD on the premises of manufacture (or on premises in the immediate vicinity) provided that the use of the IVD is intrinsic to the operation of the health institution, and not for some extraneous purpose that does not form part of the health functions of the institution. If these conditions are satisfied, it is irrelevant that a diagnostic service is being provided to a different legal entity – the exemption will still apply.

Points of clarification:

Reference to the IVD directive

There appears to be a mistake in reference to the IVD directive (98/79/EC). The directive states that an IVD must be CE marked only if/when placed on the market – not during an academic trial.

KRAS testing to predict cetuximab response

The example of KRAS testing for cetuximab response is used. We would like to clarify that it is KRAS wild-type patients that benefit from cetuximab, rather than KRAS mutant patients.

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