Genetic testing in Europe
A Network for test development, harmonization, validation and standardization of services
2005-2009

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IVDD and Genetic Testing

• Report of a workshop
• held in Leuven April 24, 2007

• David Barton
The IVD Directive

• Issued 1998
• Came into full force November 2003
• Single-market instrument
  • Access to a common internal market
  • Trade facilitation and regulatory convergence
  • Competitiveness of industry
• 3 Levels of Scrutiny: Essential Requirements plus
  1. Notification only
  3. Annex II, List B – immediate and serious risk
# Workshop Participants

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Points from Workshop

• Industry happy with IVDD
  – Right balance regulation vs. safety
  – Would like clarity on in-house exemption

• Public Health specialists less happy
  – IVDD focuses on non-maleficience, needs to focus more on beneficience
  – Risk classification must include clinical utility

• In-house exemption still controversial
  • Favoured by specialist labs
  • Frowned upon by industry, DG Health
  • Interpreted differently in different states
Proposal

• Numerous published European reports and recommendations for the regulation of genetic tests
  • None have been implemented
• Policy consensus that genetic tests should not enter routine clinical practice without thorough independent evaluation
  • Not matched by regulation at European level
• Why not an “EMEA” for IVDs?
  • Use ACCE (Analytic validity, Clinical validity, Clinical utility, Ethical, legal and social implications) approach
RMs: Selected Relevant Directive Text

(9) .... calibrators and control materials needed by the user to establish or verify performances of devices are in vitro diagnostic medical devices”

1(b) 'in vitro diagnostic medical device` means any medical device which is a reagent, reagent product, calibrator, control material...

1(i) 'placing on the market` means the first making available in return for payment or free of charge of a device......
Transfer of control materials between labs

Why?

• Many genetic disorders are very rare
• Particular mutations may be unique to a single family
• Family members may be living in different regions or countries
• Best practice is to run a positive control when testing for a specific mutation
• Such a positive control may only be available from another laboratory
• Labs do not charge each other for such materials
Scenario presented to Commission

Scenario on the exchange between testing labs of materials for use as controls developed and submitted to DG Enterprise:

Lab A sends DNA from the index case in a breast cancer family to Lab B for use as a positive control for a predictive test.

- Are such materials covered by the directive?
- Does it matter if the receiving lab is using an in-house assay or a CE-marked IVD?
NGRL Wessex approach to MHRA

A. Plasmids containing mutations developed to determine the performance of mutation detection systems.

B. Plasmids developed containing mutation controls for specific cancer genes

Questions:

1. For distribution or selling to European laboratories should these reagents be considered IVDs under the Directive, and thus require CE marking?

2. Would these reagents require CE marking if they were incorporated into UK or European external quality control assessment programs?
MHRA Response

- EQA materials are excluded from the Directive
- Calibrators and control materials that are needed to establish or verify the performance of other devices are considered to be IVD’s and will come within the remit of the regulations
- It will therefore depend on the intended purpose
- General control materials for specific genes with a diagnostic purpose made available outside an EQA scheme to establish or verify performance of devices are likely to be IVDs
A Good Balance?

If a CE-marked IVD exists for a target, reference materials specific for that target should also be CE-marked.

If no CE-marked IVD exists for a target, then RMs for that target are not establishing the performance of a “device”, and thus do not require CE-marking.

*If there is commercial demand for an assay, there should be matching commercial demand for associated RMs*

But: What if the RM is on the market *before* the IVD?