Developing diagnostics – the regulatory picture

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Today’s talk

• A little about the MHRA
• The regulatory process for IVDs
• Changes on the horizon
  – Clinical evidence & performance evaluation
  – ‘In-house’ development of diagnostics
• Q&A
About the MHRA

Executive Agency
• Government Trading Fund and an Executive Agency of the Department of Health and Social Care

Size
• Around 1300 staff, with a total budget of approximately £160 million
**Clinical Practice Research Datalink**
- NHS observational data and interventional research service
- Jointly funded by NIHR and MHRA
- Anonymised data
- Observational research studies: links between things like diet, or family history, and particular illnesses
- Clinical trials: UK/pan-EU

**National Institute for Biological Standards and Control**
- Standardization and control of biological medicines
- Over 90% of international biological standards
- UK’s Official Medicines Control Laboratory for biological medicines
- Research
- Close relationship with WHO
- WHO collaborating center for polio, influenza and HIV

**Medicines and Healthcare Products Regulatory Agency**
- Regulation of medicines: quality, safety, efficacy
- Medical devices: overseeing the UK Notified Bodies
- Operating vigilance systems
- Blood and blood products
- Quality surveillance system
- Regulating clinical trials
- British Pharmacopoeia
Regulation in the bigger picture
Medical devices legislation

• Legislation – three EU Directives

Medical Devices Directive
Active Implantable Medical Devices Directive
In-Vitro Diagnostic Devices Directive
What’s an IVD?

Rocket science is for kids
Bioinformatics is for scientists
The regulatory cycle

Diagnostic development (incl. classification) → Conformity assessment & clinical evaluation

Post-market surveillance & vigilance → CE marking

Pre-market

Post-market
Classification

Pre-market

Diagnostic development
(incl. classification)

Conformity assessment
& clinical evaluation

Post-market surveillance
& vigilance

CE marking

Post-market
Classification - IVDs

- Annex II List A
- Annex II List B
- Self Test
- General

IVDD Classification

- HIV, Hepatitis ABO Blood Grouping
- Rubella, PSA, Self Test for Blood Glucose
- Pregnancy, Cholesterol Home Tests
- Tests for Hormones, Cardiac Markers, Hematology and Clinical Chemistry Tests

Examples
Conformity assessment

Diagnostic development (incl. classification) → Conformity assessment & clinical evaluation

Pre-market

Post-market surveillance & vigilance → CE marking

Post-market
Conformity assessment

• Directives set out ‘essential requirements’ that manufacturers must meet
  ✓ Benefits must outweigh risks and achieve the claimed performance
  ✓ Analytical & diagnostic sensitivity
  ✓ Analytical & diagnostic specificity
  ✓ Accuracy
  ✓ Repeatability
  ✓ Reproducibility

• Manufacturer prepares technical documentation to demonstrate conformity with essential requirements

• Use of harmonised standards
Notified bodies
Notified body involvement

IVDD Classification

Examples

Annex II List A
- Notified Body Required
  - Design Dossier Review (Including Compliance to the CTS)
  - Audit of Quality Management System
  - Batch Released by the Notified Body

HIV, Hepatitis ABO Blood Grouping

Annex II List B
- Notified Body Required
  - Audit of Technical Documentation & Quality Management System

Rubella, PSA, Self Test for Blood Glucose

Self Test
- Notified Body Required
  - Review of Design & Labeling for Lay User Suitability

Pregnancy, Cholesterol Home Tests

General
- No Notified Body Required
  - Manufacturer Self Declares

Tests for Hormones, Cardiac Markers, Hematology and Clinical Chemistry Tests
CE marking

- Diagnostic development (incl. classification)
- Conformity assessment & clinical evaluation
- Post-market surveillance & vigilance
- Post-market

Pre-market

CE marking
CE marking

• Following successful conformity assessment, a manufacturer draws up a **declaration of conformity** and places a CE mark on the device – can be marketed anywhere in the EU

• CE mark not unique to medical devices

• ‘New Legislative Framework’ sets out common approach across a number of products sectors

• **But** standards involved vary substantially
Post-market surveillance & vigilance

Diagnostic development (incl. classification) → Conformity assessment & clinical evaluation → CE marking → Post-market surveillance & vigilance
Post-market surveillance & vigilance

Post-market surveillance – preventative/proactive

• ensure ongoing performance of device – appropriate/risk benefit balance

• inform development of future iterations of the device

Vigilance – reactive

• reporting of serious incidents

• voluntary & mandatory reporting
**MHRA – our role**

- **Advice**
  - Diagnostic development (incl. classification)
  - Post-market surveillance & vigilance
- **Study approvals**
  - Conformity assessment & clinical evaluation
  - CE marking
  - Registration of products
  - UK notified body oversight
  - Compliance
  - Safety
Exciting times

Medtech patents overtake transport as UK's biggest technology field

European patents for medical technology from the UK increased by 7.1% in 2017, overtaking transport as the UK's major technology field.

The figure comes from the European Patent Office's (EPO) annual report, which highlights the number of patents filed across Europe in 2017.
More exciting times

Diagnostic development (incl. classification)

Conformity assessment & clinical evaluation

CE marking

Post-market surveillance & vigilance

Pre-market assessment

Revision of the Medical Devices Directives
New classification rules
The quantum leap
Clinical evidence

“Confirmation of conformity with relevant general safety and performance requirements shall be based on scientific validity, analytical and clinical performance data providing sufficient clinical evidence.

“The manufacturer shall specify and justify the level of the clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose.

“To that end, manufacturers shall plan, conduct and document a performance evaluation.”
Terminology

**Scientific validity**: the association of an analyte to a clinical condition or a physiological state

**Analytical performance**: the ability of an IVD to correctly detect or measure a particular analyte

**Clinical performance**: the ability of an IVD to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with target population and intended user
Clinical evidence vs clinical utility

CLINICAL EVIDENCE
- Analytical Performance

CLINICAL UTILITY
- Scientific Validity
- Clinical Performance
So…

All IVDs will need a new performance **evaluation**, which must be updated throughout the lifecycle of the product.

Not all IVDs will need a new performance **study**.
Performance studies

New concept – when gathering data to support CE marking

General requirements on all studies

Specific requirements – including competent authority approval
  – on:
    • ‘interventional’ studies – affecting patient management decisions; and
    • studies that involve invasive procedures or other risks for patients.
Health Institution Exemption

"Devices which are manufactured by health institutions and used only on their own patients (‘in-house manufacture’) are exempt from the requirements of the Medical Devices Regulations 2002."
Health Institution Exemption

Exemption for devices used in the same health institution as they are made or modified provided:

- The exemption is justified
- An appropriate quality system is in place
- Some information is made publicly available
- The device meets all relevant GSPR
- (additional documentation requirements for some IVDs)

Summary

MHRA is developing guidance for health institutions wishing to apply the exemption to the new in vitro diagnostic medical device regulation (2017/746) and the new medical device regulation (2017/745).

This consultation closes at 5pm on 31 March 2019
In summary…

Device for performance evaluation

Performance evaluation study

Scientific Validity
Analytical performance
Clinical performance

MHRA assessment

Interventional study

EMA assessment

Companion Diagnostic

NB assessment

CE mark

Clinical Use

Health Institution
Thank you

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