Pharmacogenetics and Stratified Medicine Network Conference

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Regulatory perspectives

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Challenges for a 21st Century Regulator

• Advances in biology and biotech medicines, advanced therapies, biosimilars, combination products and precision/personalised medicines, complex devices, borderline products

• Perception about regulation causing delays/blockages(costs of bringing innovative products to market

• Global population changes
  – Ageing population
  – Co-morbidities
  – Long term conditions

• Globalisation of manufacture and supply chains

• Changing healthcare landscape and public health priorities eg antimicrobial resistance, dementia, early access
MHRA

- Executive Agency of the Department of Health (Trading Fund)
- Directly accountable to the Secretary-of-State for Health
- UK wide responsibilities (England, Scotland, Wales, N Ireland)
- Close relationship with EMA (Canary Wharf in London)

Three Centres:

MHRA Regulatory

Clinical Practice Research Datalink (CPRD)

National Institute for Biological Standards and Control (NIBSC)
MHRA 3 Centres

MHRA Regulatory
- Regulates medicines and medical devices, ensuring that they work, and are acceptably safe; focusing on the core activities of product licensing, inspection and enforcement, pharmacovigilance, and developing the British Pharmacopoeia.

Clinical Practice Research Datalink (CPRD)
- Gives access to an unparalleled resource for observational research and improving the efficiency of interventional research, across all areas of health, medicines and devices.

National Institute for Biological Standards and Control (NIBSC)
- World leaders in assuring the quality of biological medicines through product testing, developing standards and reference materials and carrying out applied research.
National Institute for Biological Standards and Control

NIBSC
NIBSC
Statutory Responsibilities for Biological Medicines

Biological Standards Act (1975): Health & Social Care Act (2011)

- “To devise and draw up standards for the purity and potency of biological substances, to design appropriate test procedures and to advise on these matters
- To prepare, approve, hold and distribute standard preparations of biological substances
- To provide or arrange for the provision of laboratory testing facilities for the testing of biological substances, to carry out such testing, to examine records of manufacture and quality control and to report on the results
- To carry out or arrange for the carrying out of research in connection with the functions referred to above
- To collaborate with WHO, European Commission and other international organisations or bodies in relation to the establishment of standards for, the provision of standard preparations of, and the testing of biological substances”
Biological Medicines

- Made from biological sources
- Highly complex
- Must be measured by biological effect
- Special risks
- Biologics a huge growth area
Medicines Control

- Independent regulatory testing required for
  - Vaccines, Blood-derived products, Biotherapeutics

- NIBSC is UK Official Medicines Control Laboratory

- >3000 batches tested in 2012
World leader in international standardisation of biologics

• Originates from 1920’s work of Dale (Medical Research Council)

• >95% WHO global measurement standards developed by NIBSC

• Centre for Biological Reference Materials
• Influenza Resource Centre
• UK Stem Cell Bank
• CJD Resource Centre
• HIV Resource Centre
Biologics Research at NIBSC

• Supporting the development of novel/improved products
  – Novel Vaccines
  – Biosimilars
  – Immunotherapeutics
  – Recombinant antibodies
• Understanding product safety signals
• Developing improved methods for measuring products
• Developing improved vaccine strains
• Improved adventitious agent testing
Advising and responding: some examples

- MMR (1999-05)
- BSE/vCJD (2001)
- Northwick Park trial (2006)
- Pandemic flu (2009, ongoing)
- HPV vaccine scare (2009)
- HIV in 60’s blood products (2009)
- Heparin contamination (2009/10)
- Cancer vaccine shortage (2012)
- Counterfeit seizures (ongoing)
Summary

• Biologics market growing rapidly
  – Many new and complex classes of biologics in development, e.g. regenerative medicines, genomic medicine
  – Tremendous opportunities but significant regulatory challenges

• A strong supporting regulatory science base is essential to support innovation, protect health

• NIBSC sets the international standard for biologics
  – Unique scientific expertise and facilities
  – Excellent reputation, very strong global partnerships

• 2014, Division of Advanced Therapeutic Products
Clinical Practice Research Datalink

CPRD
• High quality, longitudinal, electronic healthcare data for academic and commercial research use

• Primary care and links to secondary care (Ethics permission for 50 datasets, actual datasets possible now ~ 8)

• Effectively anonymised healthcare records on 12.6m patients

• Data on 54m people: Hospital Episode Statistics, cancer registries, Myocardial Ischaemia National Audit Project (MINAP), national air pollution, central mortality data.
CPRD Data enables

• Pharmacovigilance
• Pharmacoepidemiology
• Interventional studies
• Outcomes
• Pharmaco-economics
• Improved methodologies in Clinical Trials
Services for Interventional Studies

• Trial feasibility and recruitment; trial optimisation
• Randomisation at point of care
• Healthcare records for medical history and follow up of patients in trials
• Links to more formal trials to give longitudinal data/outcome data
• Adaptive trial design
Trialviz

• Trialviz is a new web-based tool that enables MHRA staff to contact suitable patients through primary care practices to see if they will consent to be recruited to trials.

• Key steps in the Clinical Trial process will be significantly faster and more accurate, making clinical trials conducted in the UK far more efficient and cost effective.

• Enter the inclusion and exclusion criteria for your trial into Trialviz and it will locate patients meeting the criteria.
CPRD Trialviz showing where the patients are by “large population” regions
Trialviz World Visualizer

- Trialviz World Visualiser illustrates top level data on the potential number of patients who meet criteria in different countries and regions.
Regulatory use of CPRD data – vaccine examples

- **HPV and chronic fatigue syndrome** – used CPRD data on background rates of CFS to put Yellow Card spontaneous reports into context in real time and respond to media and patient concerns.

- Followed up by controlled epidemiological study – no increased risk found.

- **Pertussis vaccine for whooping cough** – very little pre- or post-licensing data on use in pregnancy, range of pre-specified events all of which occur naturally in the third trimester.

- MHRA did a proactive study in CPRD (developed a cohort of vaccinated women and matched to unvaccinated historical cohort).

- Using CPRD records identified over 18,000 women vaccinated within 6 months.

  - no increased risk found
the challenge of bringing innovative products safely to the market with earlier access for patients with unmet needs
The regulatory response to the challenge of bringing innovation safely to the market

• The new **UK Early Access to Medicines Scheme** and **EU Adaptive Licensing Scheme** complement each other:

  – **Early Access to Medicines Scheme (EAMS)** to enable responsible prescribing of innovative medicines in areas of unmet need whilst they are unlicensed or used off-label; UK-only

  – **Adaptive Licensing (AL)** seeks to make the point of first licensing using narrower, potentially smaller data sets which may be earlier in the development process; EU level. The same products will often meet the criteria for both schemes
EAMS Process (UK only)
Promising Innovative Medicine (PIM) designation

• Under **EAMS Step 1**, a Promising Innovative Medicine (PIM) designation provides an early indication that a product may be a possible candidate for EAMS:

  – Designation based on early clinical data (for example from phase II studies)
  – Designation could occur several years before licensing
  – Designation will be issued after an MHRA designation scientific meeting

• Open to new biological or chemical entities as well as repurposing of established or recently approved drugs
EAMS scientific opinion

• Under **EAMS Step 2**, MHRA would issue a new benefit:risk scientific opinion that will support the prescriber to make a decision with the patient on using this medicine, when still unlicensed or used off-label:
  – Opinion could support access by patients to innovative medicines (outside clinical trials) earlier in development process
  – Where compelling evidence exists, opinion could be given on the basis of phase II studies instead of phase III
EU Adaptive licensing

- MHRA contributed to the development of the EMA’s Adaptive Licensing pilot launched by the EMA in March

- Aim is to provide a framework for informal discussions between companies and regulators in a “safe harbour” environment

- Will allow exploration of the strengths and weaknesses of all options for development, assessment, licensing, reimbursement, monitoring, and utilisation pathways in a confidential manner and without commitment from either side
MHRA Innovation Office

• Face-to-face discussions with ‘customised’ teams of MHRA advisors from across the centres, no commitments on either side

• Both Scientific and Regulatory Advice

• Joint meetings possible with MHRA and NICE

• Joint meetings possible with MHRA and EMA
Conclusions

• Rapidly changing environment….regulators, researchers and companies must evolve to meet the challenges

• Effective and responsible use of data is key to successful surveillance of patients who are given medicines earlier in the development process

• CPRD can enhance development by locating patients suitable to enrol in trials – benefits for companies and patients

• NIBSC capabilities in new molecular and cellular biologics are second to none…and new Division of Advanced Therapeutic Products

• MHRA very well placed to meet future challenges using synergies between its three centres: Regulatory, CPRD and NIBSC
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COMMUNICATE AT EARLY STAGE