Medicines & Healthcare products Regulatory Agency

Facilitating the use of biomarkers in early drug development: the role of regulators

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Disclaimer

These views should be understood as my own and do not necessarily reflect the official position of the MHRA, EMA or EMA committees or working parties

Outline

- A brief introduction to the Regulatory Framework in Europe
  - Medicines & Health Care Products Regulatory Agency (**MHRA**)
  - European Medicines Agency (**EMA**)
- Regulatory input in early drug development
  - Process for qualification of biomarkers
- Use of biomarkers in early drug development
  - Examples of biomarkers led drug development

About the MHRA

The **MHRA** is the Competent Authority (CA) for the UK and is seen as a regulator of authority within Europe. MHRA acts as Reference Member State (RMS) for a high proportion of Marketing Authorisation Applications (MAAs).

There are many divisions within the MHRA e.g. Licencing, Devices, and Vigilance and Risks Management Medicines (VRMM).

Some or the MHRA activities include:

- Assessment of the safety, efficacy, quality of medicines and authorising their sale in the UK for human use (Licencing Division).
- Regulation of clinical trials of medicines and medical devices (Licencing and Devices).
- Provision of scientific, technical and regulatory advice on medicines and medical devices (Licencing and Devices).
- Conducting post-marketing surveillance (VRMM).

Regulating clinical trials

There is a risk associated will all trials. The MHRA is responsible for authorisation of clinical trials in the UK.

According to the current legislation, clinical trials of medicinal products in human subjects require:

1. Authorisation by the competent authority (MHRA in the UK);
2. Favourable opinion by an ethics committee, including any local site approvals (e.g. NHS in UK)

Clinical trials should follow regulatory guidelines.

EMA released a new guideline for First-in-Human (FIH) and early phase studies:

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products”

About EMA

The European Medicines Agency (**EMA**) is an agency of the European Union (EU) responsible for scientific evaluation, supervision, and safety monitoring of medicines in the EU.

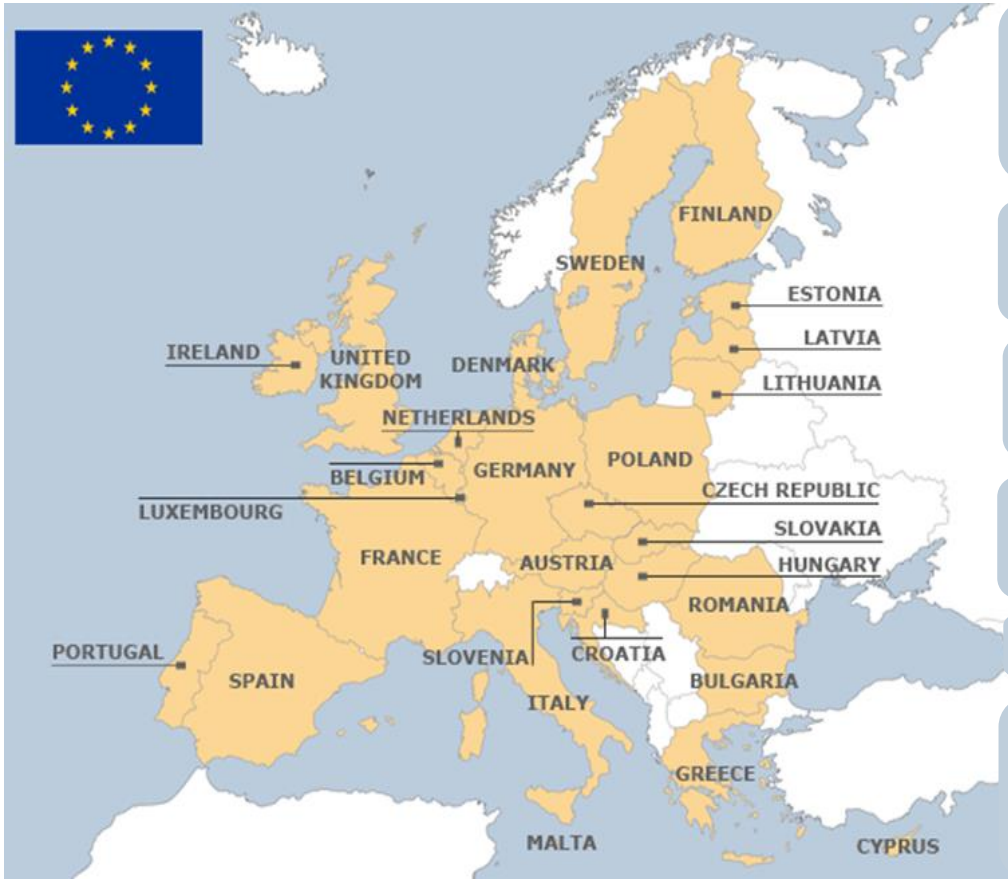
Member States (**MS**) & **EMA** work together in a regulatory network of over 4000 ‘external’ European experts.

The **EMA** co-ordinates, through its scientific committees, the evaluation of Marketing Authorisation Applications and liaises with **MS**.

Scientific committees consist of experts from national competent authorities, patient representatives and healthcare-professional organisations.

The Committee for Medicinal Products for Human use (**CHMP**), and its working parties (**WP**) e.g. Biostatistics Working Party (**BSWP**) contribute to the development of medicines and medicine regulations by providing scientific advice and preparing scientific guidelines.

MHRA in the European Union



28 Member States in European Union + EEA countries (almost 500 million people)

Legislation set up at European Union level

Medical Devices: authorisation always for the whole EU

Medicines: authorisation nationally, whole EU/EEA or number of countries

European Medicines Agency (EMA)

Heads of Medicines Agencies network (uniting 45 regulators from 31 countries)

What do statisticians do at the MHRA?

Statisticians work as part of a multidisciplinary team across different therapeutic areas. Statistical expertise is also available on request to Clinical Trials Unit (CTU) and Devices Division.

There are two main areas where we are involved.

- We provide statistical assessment of dossiers submitted via National or European Procedures.

- We provide scientific advice upon request at both national and European levels e.g. through CHMP scientific advice.

Examples of what we look for

Statistical input is tailored depending on the task; scientific advice or assessment of dossiers and stage of drug development (early vs. late). Below are some general principles.

- Is the study design in line with the trial objectives?
- Is the sample size adequate for the trial's objectives?
- Has randomisation been carried out correctly or has it been compromised in anyway?
- Have premature discontinuations been handled appropriately?
- Have the statistical methods been correctly pre-specified?
- Have the statistical guidelines (ICH and CHMP) been followed appropriately?
- Is the evidence generated robust?

CHMP and ICH guidelines are available on the EMA website

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000602.jsp&mid=WC0b01ac05807d91a4

Emerging trends from interactions with companies

Clinical developments are changing; fewer patient available for efficacy and safety evaluation, relying on more innovative approaches.

Some examples of emerging trends:

- Increasing practice to perform FIH and early phase clinical trials with integrated protocols that combine a number of different study parts.
- New innovative trial designs are emerging for example umbrella and basket trials. These trials play a key role in the development of stratified medicines.
- Increasing use of adaptive design combining a proof-of-concept study and a dose-finding study.
- Rising number of advanced therapy medicinal products (ATMPs), made from tissues, genes, or cells, which may offer ground-breaking new treatment opportunities for many conditions.
- Stratified medicines are becoming increasingly important, particularly but not only in oncology.

Regulatory input in early drug development

The **MHRA** innovation office provides access to world-class knowledge, expertise, and experience from specialists across the agency.

Companies recognise that **MS** have their own expertise. Some companies seek parallel advice (scientific and regulatory) from the **EMA** in the EU and Food and Drug Administration (**FDA**) in the US. Joint advice is also available with other stakeholders for example the Health Technology Assessment (HTA).

Regulators are open to engaging on a broad range of novel approaches not limited to the use of biomarkers. The **EMA** qualification process addresses innovative development and tools. A similar process exists in the **FDA**.

Details of the qualification procedure are available from the **EMA** website

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0#section2

Process for qualification of biomarkers

The **EMA** qualification process was launched in 2009. Qualification can contribute to acceptance and application of the new method across multiple drug development programs.

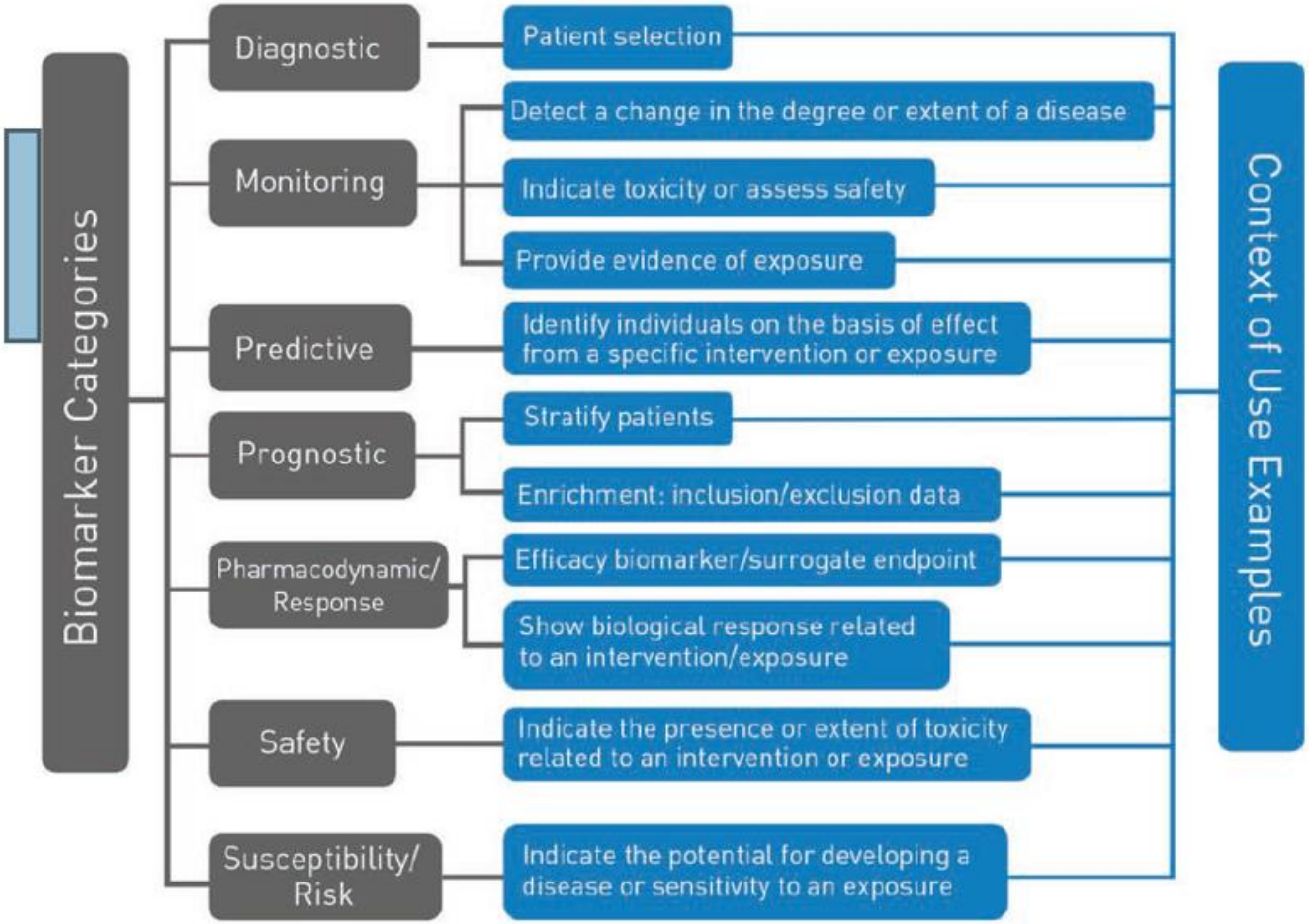
This qualification process leads to a CHMP **qualification opinion (public)** or CHMP **qualification advice (confidential)**, on the basis of advice from the Scientific Advice Working Party (SAWP).

Qualifications examples:

- Total kidney volume (TKV) as a prognostic biomarker for use in clinical trials evaluating patients with autosomal dominant polycystic kidney disease (ADPKD), adopted in 2015.

- **M**ultiple **C**omparison **P**rocedure – **Mod**eling (MCP-Mod) as an efficient statistical methodology for model-based design and analysis of phase-II dose-finding studies under model uncertainty, adopted in 2014.

Types of biomarkers and context of use



Source: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/UCM531522.pdf

Use of biomarkers in early drug development

Biomarkers are used to enable better decision making during drug development but are less well accepted as surrogate endpoints for Phase III studies.

Examples of well established biomarkers (clinical endpoint):

- Blood pressure (stroke, heart failure)
- HIV viral load (survival)

Biomarkers can be used to monitor drug activity, to identify early sign of toxicity, to optimise dose regimen, and for enrichment of patients population.

Pharmacodynamic (**PD**) biomarkers constitute the majority of biomarkers in early drug development (pre-clinical, Phase I, and Phase II).

The European Medicines Agency (EMA) has released for public consultation a concept paper on the development and lifecycle of personalised medicines and companion diagnostics that measure predictive biomarkers which help to assess the most likely response to a particular treatment.

Examples of Biomarkers in use

Diagnostic biomarker: Testing for HER2 prior to initiation of therapy with Herceptin (trastuzumab) in patients with metastatic breast cancer.

Monitoring biomarker: Prothrombin time used for warfarin therapeutic monitoring.

Prognostic biomarker: Total Kidney Volume for use in clinical trials evaluating patients with autosomal polycystic kidney disease.

Enrichment biomarker: Cerebrospinal-fluid amyloid beta 1-42 for use in clinical trials to identify patients with mild and moderate Alzheimer's disease.

***Safety biomarker*:** Screening for carriage of HLA-B*5701 allele in any HIV infected patients, irrespective of racial origin, before initiating treatment with Abacavir (antiretroviral therapy).

Biomarker led drug development – Example 1

A new type of treatment that tackle the underlying cause of cystic fibrosis (CF), the genetic defect, rather than just the symptoms.

CF is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene that result in absent or deficient function of the CFTR protein at the cell surface.

Orkambi is a fixed dose combination of ivacaftor (IV) and lumacaftor (LUM).

Early studies demonstrated that that pharmacologic modulation of CFTR function through treatment with LUM/IVA combination therapy can result in clinical benefit in subjects who are homozygous for the F508del-CFTR mutation, and confirmed that LUM monotherapy did not provide clinically meaningful benefit in these subjects.

The company had interaction with both the US and EU regulatory authorities. The product was approved in the EU in 2015.

Biomarker led drug development – Example 2

Use of nivolumab as monotherapy in combination with ipilimumab for the treatment of advanced melanoma in adults.

PD-L1 expression in tumour was used as biomarker to stratify patients.

The benefit of the treatment combination in terms of PFS was only demonstrated for patients with low PD-L1 compared to nivolumab alone.

Key regulatory question: To what extent should PD-L1 status be used to indicate clinical benefit of the combination treatment?

Answer: refer to the EPAR for procedure: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/003985/WC500209378.pdf

Summary and conclusion

- Regulators are open to engaging with companies at all stages of the clinical development for all potential uses of biomarkers.
- Novel methodologies can be incorporated into drug development through the qualification procedures.
- MHRA has a range of opportunities for innovators to seek advice.
- Regulators want to bring medicines to patients faster, where appropriate. But regulatory approval does not necessarily confer commercial availability.

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Thank you for listening

Any questions?

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