Medicines & Healthcare products Regulatory Agency

Continuity in uncertain times: MHRA Brexit provisions

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CPRD NIBSC MHRA

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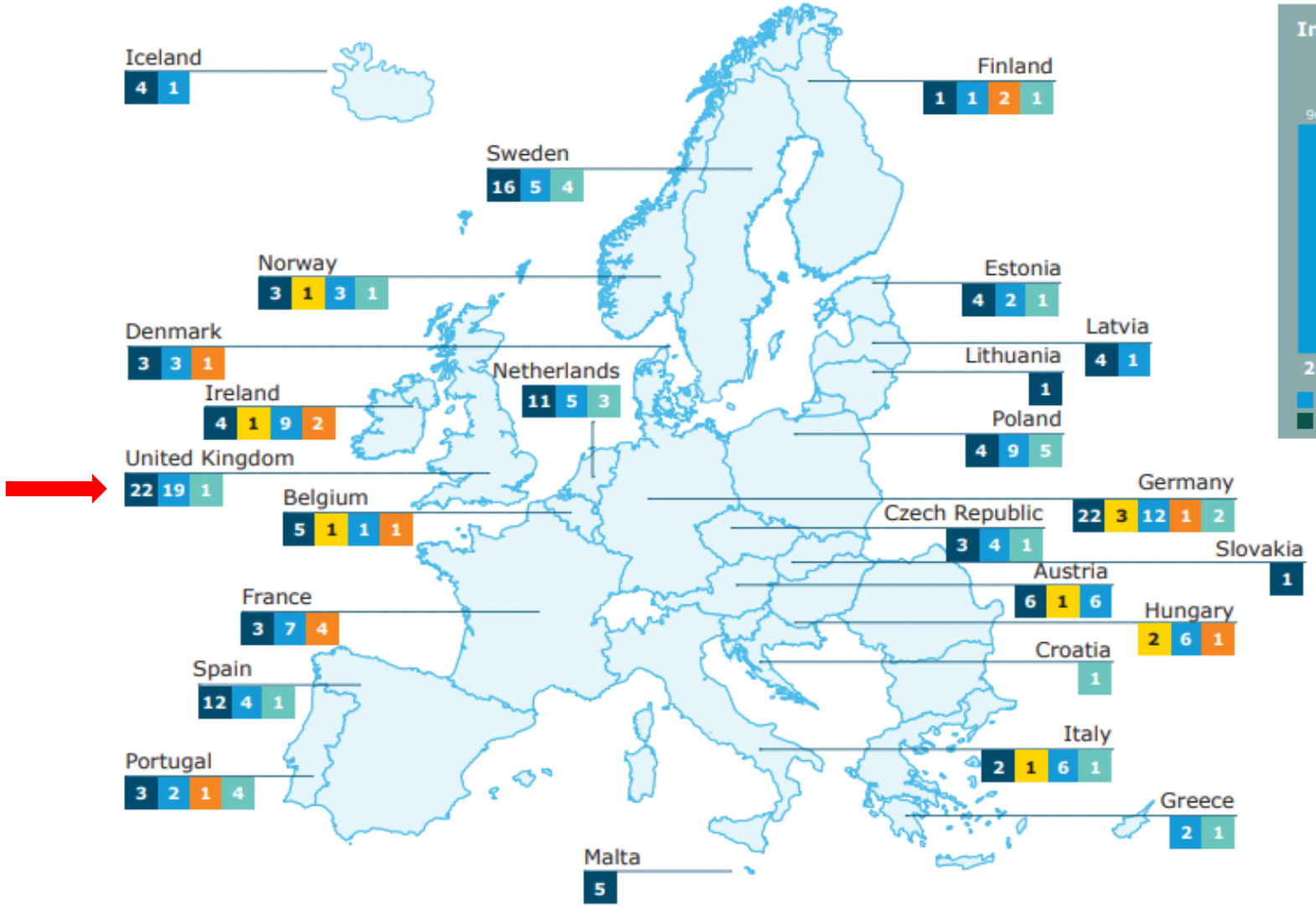
Medicines & Healthcare products Regulatory Agency

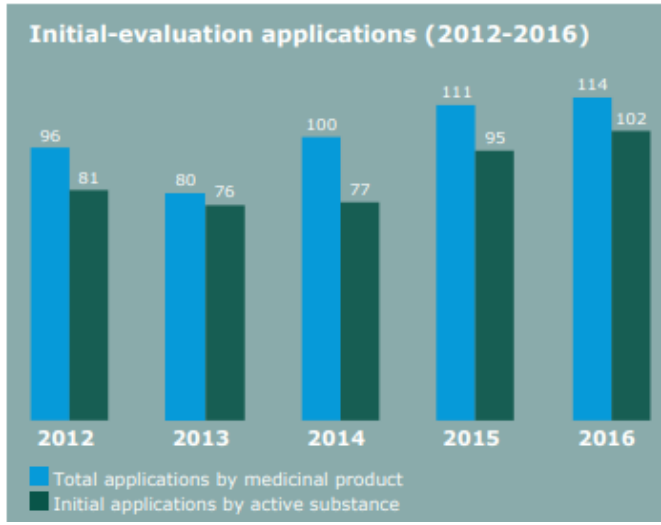
Mission and Overview

"We **protect and improve** the health of millions of people every day through the effective regulation of medicines and medical devices, underpinned by science and research"

- Government trading fund and an executive agency of the Department of Health and Social Care (DHSC)
- Around 1350 staff

The past: UK Rapporteurships with the EMA





EMA annual report 2016

Rapporteur regular
Rapporteur MNT
Co-rapporteur regular
Co-rapporteur MNT
Assessor part of MNT

The future:

Brexit timeline: 23:00 GMT on 31 October 2019

Scenarios:

1. **DEAL** - Ratification of withdrawal agreement
   UK and MHRA in Transition Period
   until 31 December 2020

2. **NO DEAL** – MHRA as freestanding regulator from
   1 November 2019

No deal preparations:

- Statutory instruments passed by parliament
- Guidance on MHRA website
- Grandfathering of EMA licenses
- Transitional arrangements: Different options for ‘in-flight’ procedures
- Additional provisions
- Standard assessment pathway
- New assessment routes

Statutory instruments

- Amending Regulations will come into force immediately before exit day in case of a no deal scenario
- They are a direct translation of EU law into UK law amending relevant legislation, replacing reference to European bodies with UK ones
- Transposed legislation
  - 2001/83/EC and amending legislation (Medicines Directive)
  - 2001/20/EC and amending legislation (Clinical Trials)
  - Medical Devices Regulation (EU) 745/2017
  - In-vitro Diagnostic Devices Regulation (EU) 746/2017

Medicines and Devices

- The Human Medicines (Amendment etc.) (EU Exit) Regulations 2019
  http://www.legislation.gov.uk/ukdsi/2019/9780111179185/regulation/3
- The Medical Devices (Amendment etc.) (EU Exit) Regulations 2019
  https://www.legislation.gov.uk/ukdsi/2019/9780111179260/contents
- The Human Medicines (Amendment etc.) (EU Exit) (No. 2) and the Medical Devices (Amendment etc.) (EU Exit) (No. 2) Regulations 2019

  https://www.gov.uk/eu-withdrawal-act-2018-statutory-instruments/the-human-medicines-amendment-etc-eu-exit-no-2-and-the-medical-devices-amendment-etc-eu-exit-no-2-regulations-2019

  Amending:

  Human Medicines Regulations 2012

  Medicines (Fees) Regulations 2016

  Medical Devices Regulations 2002

Clinical Trials

- The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019
  http://www.legislation.gov.uk/uksi/2019/744/contents/made

Amending

Medicines for Human Use (Clinical Trials) Regulations 2004

ATMP provision 1394/2007 Art 2 (1)(b)

- Tissue Engineered Product definition, last paragraph relating to non-viable cells:

original:

Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.

transposition:

A product is not a tissue engineered product if it—

(a)contains or consists exclusively of non-viable human or animal cells or tissues;

(b)does not contain any viable cells or tissues; and

(c)does not act principally by pharmacological, immunological or metabolic action

The meaning is maintained!

MHRA guidance

https://www.gov.uk/government/collections/mhra-guidance-and-publications-on-a-possible-no-deal-scenario

capconversions@mhra.gov.uk

No deal - guiding principles at MHRA

- MHRA aims to complete procedures no later than EMA and European decisions
- Alignment with European timelines: Renewals, orphan designations etc.
- European Guidelines continue to apply as they stand on exit day

Underpinned by MHRA and EU mutual recognition agreements and continued participation in ICH, PIC/S, ICMRA

Grandfathering for centrally authorised products (CAPs)

- Automatic conversion on exit day, no fee
- All licence holders were contacted by MHRA and issued with a licence number
- Opt-out is a possibility, latest to notify 21 days after exit day (MHRA will publish list)
- MHRA national submission portal will be ready!
- baseline eCTD submission:
  - within one year from exit day
  - required for variations, unless exceptional circumstances
- Need to establish a legal presence in the UK: before the end of 2020

https://www.gov.uk/guidance/converting-centrally-authorised-products-caps-to-uk-marketing-authorisations-mas-in-a-no-deal-scenario-grandfathering-and-managing-lifecycle-ch

Data requirements for baseline submission: Point 1 on website and ff.

Variations and Ongoing CAP variations on exit day

Ongoing variations

- Type IA: Submit with initiating sequence (inform MHRA if subsequently rejected by EMA)
- Type II: Submit with initiating sequence if positive CHMP opinion

  Submit as separate sequence if final opinion pending (assessment and fee applies)

Renewals:

- Date as per EU grant date

– for ongoing renewals: positive CHMP opinion?

New variations: at least minimal initiating sequence must have been submitted to MHRA

In-flight applications, centralised procedure

- Any EMA assessment already reported before exit day will be taken into account
- Details of handling determined by stage of the procedure
- MHRA contacted all applicants with pending applications at the beginning of April to discuss options in TC
- Same exercise will be conducted with applications if no deal remains an option in October
- However: companies that have had a TC in April will not have another TC for other products in October - contact your company's responsible regulatory person or MHRA if problems

https://www.gov.uk/guidance/guidance-on-the-handling-of-applications-for-centrally-authorised-products-caps-pending-on-exit-day

Inflight applications, CAPs ct'd

CHMP Procedure on exit day	End of Procedure (usually Day 210)	Day 181-209	Day 180	Day 121 – 179	Day 120	Day 80 - 119	Before Day 80
Application status	Application is the subject of a CHMP positive scientific opinion	Assessment of Responses	In Clock Stop List of outstanding issues available	Assessment of Responses	In Clock Stop Review of scientific data available and List of Questions sent to applicant.	Application in the first assessment phase	
Applicant action	Submit application to MHRA for determination in line with CHMP Scientific Opinion[1]	(i) Submit EU application and responses to MHRA to complete assessment tailored to outstanding issues or (ii) await CHMP opinion then ask MHRA to complete its assessment	(i) When available, submit responses and the EU application to MHRA for In-Flight Assessment or (ii) Await Day 210 CHMP opinion and submit for Targeted Assessment if eligible.			(i) Submit EU application to MHRA for independent assessment whilst CHMP assessment continues or (ii) Await CHMP opinion then submit for targeted assessment if eligible	
Fee payable	No fee	No fee	No fee			In accordance with published fee schedule	
MHRA timeline	Determination as soon as practicable after submission and not later than Commission Decision	Assessment decision followed by determination as soon as practicable and not later than Commission Decision	(i) 60-day timetable with provisional assessment decision no later than 42 days after start (aligned to published CHM schedule) (ii) Targeted assessment with provisional assessment decision 42 days after start (See guidance on targeted assessment)			In accordance with published assessment guidance	

Decentralised and Mutual Recognition Procedure

- Approved products automatically convert to national licenses
- Approved ongoing procedures within the 30 day national phase: proceed
  (negative opinion will continue to be negative…)
- Applications before decision phase: MHRA picks-up, taking previous assessments into account – no additional fee
- Procedures before d70
  - UK RMS: national procedure but within agreed timetable
  - UK CMS: full assessment report necessary

https://www.gov.uk/guidance/guidance-on-handling-of-decentralised-and-mutual-recognition-procedures-in-a-no-deal-scenario

RIS.NA@mhra.gov.uk

Current experience:

- Good uptake of TC offer for pending centralised applications
- Legal impossibility of submitting national application in parallel with centralised application should be noted

ATMPs

- Same principles continue to apply
- Data, traceability, exemptions from licensing, packaging and post-authorisation requirements will remain unchanged

- Definitions of individual classes of ATMPs will remain unchanged
- classification of ATMPs in the UK will be undertaken by the MHRA in accordance with the legislation and current guidance
- The decision on classification of a product by the European Medicines Agency may be taken into account, but the final decision on classification for products in the UK will rest with MHRA

EU Import and Export provisions for ATMPs

- Provisions of out-of-spec batches as per guideline GMP for ATMP para 11.5 will continue to apply – i.e. can continue to be supplied under that scheme

  ➔ inform MHRA when OOS for UK batch has occurred

- UK will continue to accept product released in EU
- UK will be third country to EU, and relevant provisions apply (ask local NCA)

  ➔ For licensed products CHMP/CAT can agree to waive EU release testing requirements (as per GMP for ATMP para 11.15 ff) under certain circumstances

Orphan Drugs

- For licensed EU products, will be converted
- UK will offer incentives in the form of market exclusivity and full or partial refunds for marketing authorisation fees to encourage the development of medicines in rare diseases.
- Reviewed at time of MAA not pre-designation
- Life-threateing or chronically debilitating disease with no satisfactory treatment
- Prevalence 5 in 10,000 or justify
- Up to 10 years market exclusivity, 2 additional years if based on PIP

- https://www.gov.uk/guidance/how-uk-orphan-medicinal-products-will-be-managed-in-a-no-deal-scenario

Clinical trial submissions - basics

- Clinical trials are a national competency under the current legislation, this is not impacted by Brexit
- EU and UK already accept data from trials conducted elsewhere in marketing authorisation applications
- Multi-national trials can be conducted now within the EU, or internationally – this continues

Clinical trial submissions - transparency

- UK's intention is to align transparency provisions with those currently operating in the EU
- In the short term, continue to use established international registers EudraCT (EU), ISRCTN (International Standard Randomised Controlled Trial Number) register (UK), and ClinicalTrials.gov (USA)
- Transparency measures will be strengthened under the new EU Clinical Trials Regulation (CTR) 536/2014. If this Regulation is not in force in the EU on exit day it will not be incorporated into UK law under current terms of the EU Withdrawal Act. However, we will align where possible with the CTR without delay#.
- By the time the EU's new portal goes live (as part of the new CTR), the UK will have its own equivalent hub

Clinical trial amendments

- Sponsor or legal representative in UK or approved country (EU/EEA)
- EU release site in addition to UK: no sub am.
- Country on the approved country list (includes EU/EEA) can directly supply material to UK trials
- 1 year transition period: MIA (IMP) Import authorisation required, overseen by QP, substantial amendment

Clinical Trials Regulation 2014 (EU)

Not transposed into UK law, as not applicable yet, alignment aimed for

https://www.gov.uk/guidance/guidance-on-substantial-amendments-to-a-clinical-trial-if-the-uk-leaves-the-eu-with-no-deal

New Assessment Routes:

Targeted assessment

- Intended to support timely availability of new medicines
- MHRA will evaluate the marketing authorisation application together with the Committee for Medicinal products for Human Use (CHMP) assessment reports submitted by the applicants, and will reach its opinion on approvability within 67 days of submission of a valid application to the MHRA
- **new active substance** and **biosimilars**
- Positive CHMP opinion (intended that submission is immediately after positive CHMP opinion, from d180)
- Submit Same dossier as for EMA and subsequent assessment reports
- Also for orphans, conditional and exceptional circumstances
- Submission dates to be published
- This is an independent assessment taking CHMP report into account, so approval is not automatic!

Accelerated assessment Pathway

- Enhancing availability of novel medicines
- MHRA will reach its opinion on approvability within 150 days
- Two phases: d80 AR (including orphan status), 90 clock-off, d150 AR
- available for **all products containing new active substances, including biologicals**
- Includes applications for orphans, conditional and exceptional circumstances
- Contact MHRA for submission dates

Rolling Review pathway

- new route for marketing authorisation applications intended to enhance development of novel medicines
- offering on-going regulatory input and feedback enabling the applicants to ‘get it right first time’ and reduce attrition due to avoidable regulatory pitfalls.
- phased, modular, iterative approach to evaluation of marketing authorisation applications
- available for all products containing new active substances, including biologicals

https://www.gov.uk/guidance/guidance-note-on-new-assessment-routes-in-a-no-deal-scenario#accelerated-assessment-pathway

Current Situation:

- Transition period has de facto started, this will be deducted from 2 year period should withdrawal agreement be passed
- No further Rapporteurships for UK
- Existing Rapporteuships are reassigned, but ‘knowledge transfer’ where UK was Rapp or Co-Rapp is an ongoing process
- UK continues to be represented in all Committees and Working groups
- UK still represented in drafting groups
- UK involved in ongoing projects, includes Commission initiative on GMO interplay with medicines

DEAL: Transition period

Details under negation

- No UK Rapporteurships
- UK recognises decisions taken at EMA level
- UK to participate in EMA committee if it is in the interest of patient safety for EU or UK

MHRA continues to provide:

Scientific Advice

- The MHRA will continue to offer its national scientific advice service after the UK leaves the EU
- **In the event of a no deal Brexit UK-based Small and Medium-sized Enterprises (SME) will be exempt from the fee**.

- both regulatory and scientific advice to companies on any type of medicinal product
- all aspects of development (regulatory, non-clinical, quality and clinical)
- at any stage of development; they are most useful before submission of a Marketing Authorisation
- can also be after an MA is granted e.g. concerning a variation to an existing product licence;

See MHRA website for the on-line request form at:

http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Informationforlicenceapplicants/Otherusefulservicesandinformation/Scientificadviceforlicenceapplicants/Requestforscientificadviceform/index.htm

MHRA broader scope advice

- Useful for innovative approaches that are not tied to just one development programme
  - *e.g.* novel trial design, new manufacturing process
- As approaches are new formal written answers are not given
- Informal feedback given at a face-to-face meeting

Parallel scientific advice from the MHRA and NICE

- Since April 2010.
- After a joint scientific advice meeting the MHRA and NICE will produce separate documents to answer the respective questions raised by the Company.

Early Access to Medicines

- medicines that are still being developed but cannot yet be made available as licensed treatments
- not a substitute for appropriate clinical development and inclusion of patients in well designed clinical studies remains the preferred option
- Primarily aimed at medicines that have completed Phase III trials, but may be applied to completed Phase II trials in exceptional circumstances

The criteria of suitability:

✓ High unmet need (life-threatening, seriously debilitating)

✓ product offers benefit or significant advantage over and above existing treatment options

✓ Potential adverse effects likely to be outweighed by benefit

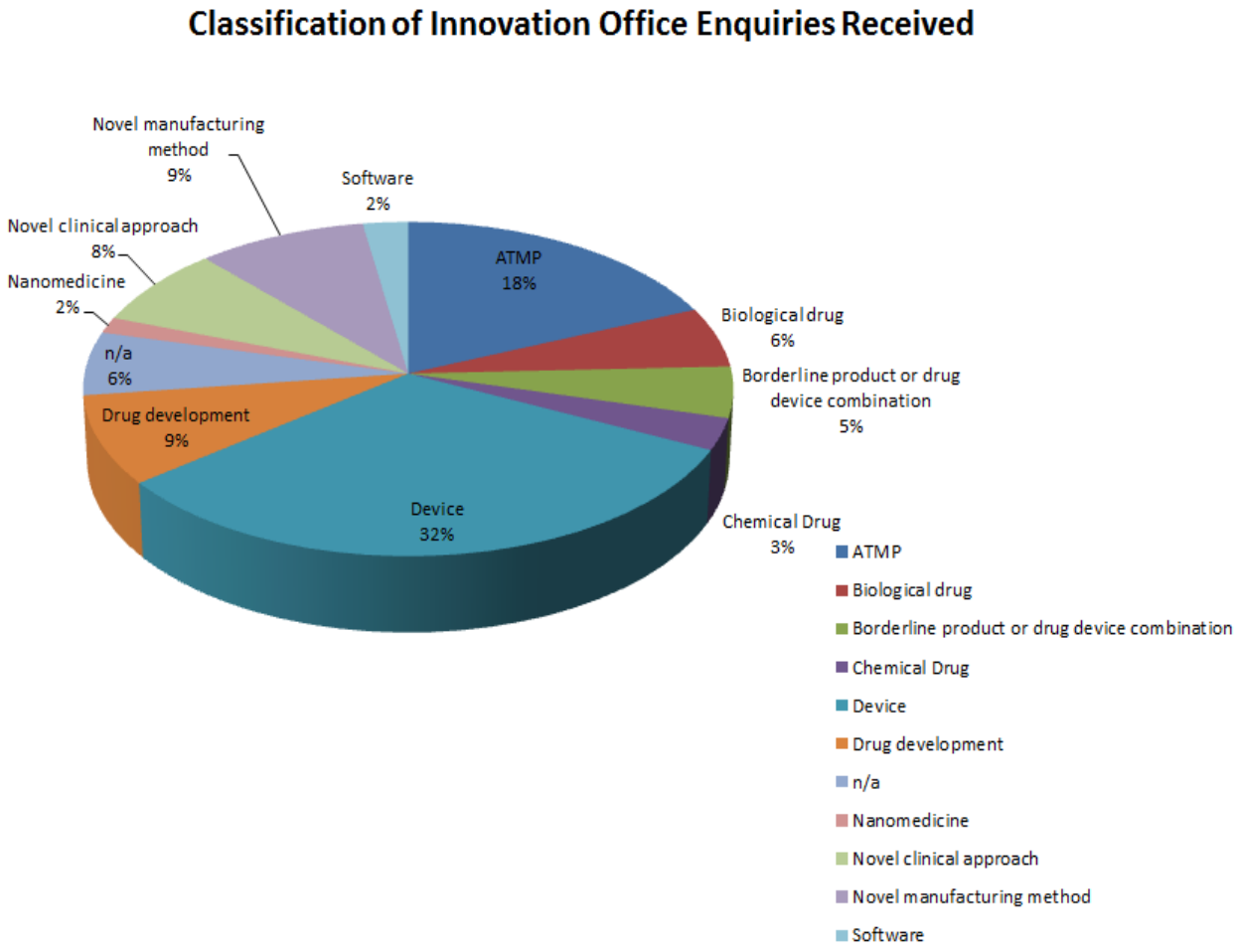
✓ The Applicant is able and willing to supply the product and to manufacture it to a consistent quality standard (GMP)

https://www.gov.uk/apply-for-the-early-access-to-medicines-scheme-eams

eams@mhra.gov.uk

Innovation Office

- Early dialogue with researchers and companies
- Clarify regulatory requirements
- All MHRA product areas
- Regulatory / informal advice or scientific advice
- At any stage of product development
- Irrespective of existing guidelines
- Case studies published to encourage enquiries https://www.gov.uk/government/groups/mhra-innovation-office#read-our-case-studies
- More than 300 enquiries received to-date



The regulatory advice service for regenerative medicine (RASRM)

- For ATMP / cell therapies / regenerative medicines
- Launched October 2014
- Hosted by MHRA Innovation office
- A cross-regulatory Agency advice source

MHRA
Regulating Medicines and Medical Devices

HTA
Human Tissue Authority

HUMAN FERTILISATION & EMBRYOLOGY AUTHORITY

NHS
Health Research Authority

Department for Environment Food & Rural Affairs

NICE National Institute for Health and Care Excellence

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Thank you!