

# Case-by-Case” Regulatory toxicology testing in Drug Development in Rare or Debilitating Disease

**David R Jones**

*Expert Pharmacotoxicologist*

**MHRA**

**[www.mhra.gov.uk](http://www.mhra.gov.uk)**

[David.jones@mhra.gsi.gov.uk](mailto:David.jones@mhra.gsi.gov.uk)

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# Medicines and Healthcare products Regulatory Agency (MHRA)

An executive agency of the Department of Health

Medicines and Healthcare  
Products Regulatory Agency



## What is the MHRA?

- The MHRA is:
- an executive agency of the Department of Health
- regulates the safety, quality, effectiveness & performance of medicines and medical devices
- employs over 800 people
- is largely funded by fee income from provision of services to industry
- runs scientific committees which advise Ministers on safety of devices and medicines
- is mainly based in Central London

## What are the MHRA Objectives?

- TO PROTECT PUBLIC HEALTH
- to provide authoritative information
- to influence international regulation
- TO SUPPORT INNOVATION AND THE DEVELOPMENT OF MEDICINES AND MEDICAL DEVICES
- to keep the cost of regulation as low as possible
- TO MAKE FACT BASED, DECISIVE JUDGEMENTS WHICH ARE IN THE INTERESTS OF PATIENTS AND CONSUMERS

# The Role of the Regulator

# The Drug Regulator's Tightrope Walk



**MHRA**  
Regulating Medicines and Medical Devices

Protect public health ...

... against negative consequences from unsafe or ineffective medicines.



... against negative consequences from failing to meet unmet medical needs.

When in doubt, be negative, “we need more information”

When in doubt, be positive, “it might be a patient's only hope”

Worry about false-positive decisions “Type-1 error”

Worry about false-negative decisions “Type-2 error”

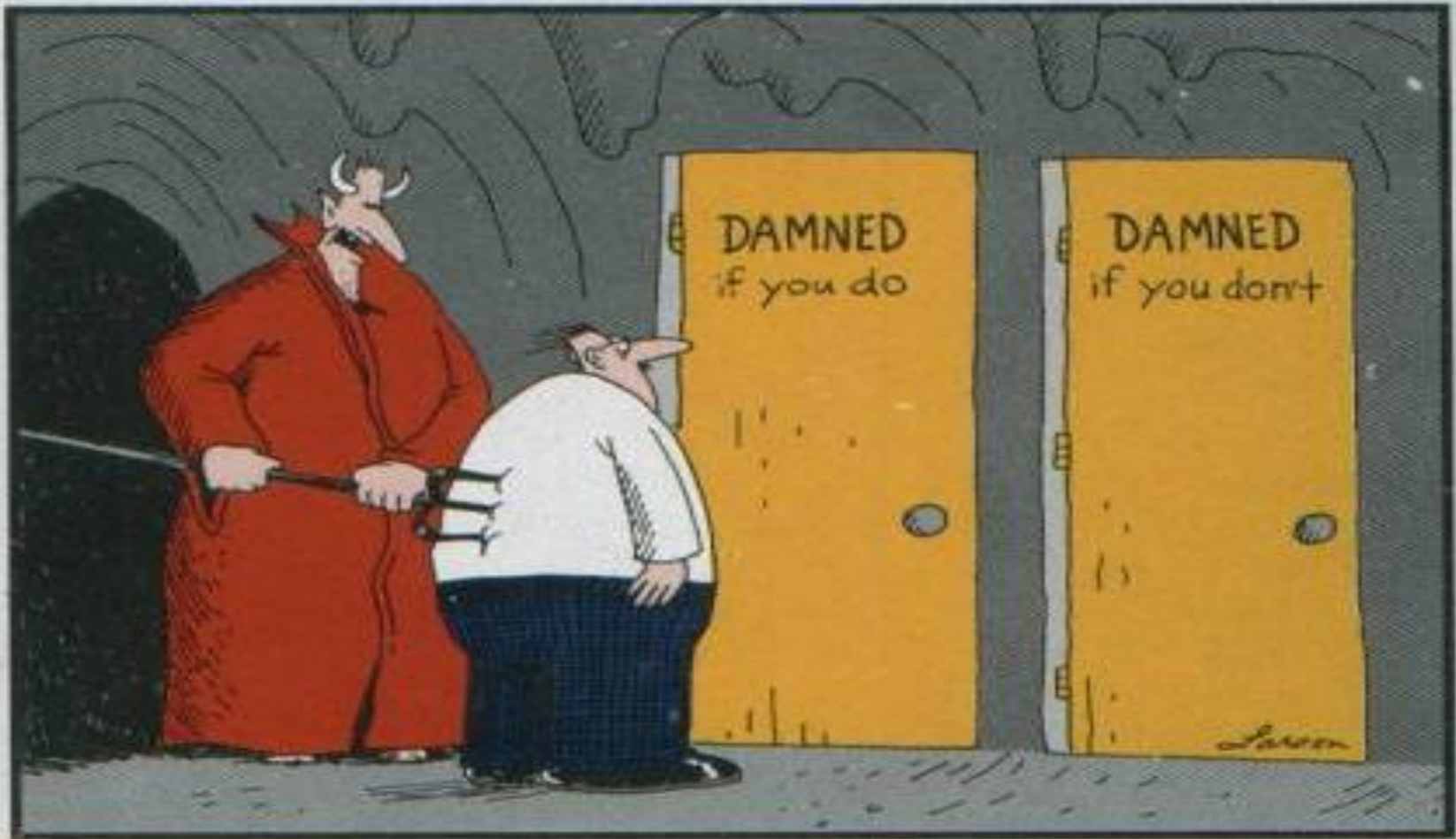
Are the (dis-)incentives balanced right to influence regulators' behaviour?

What are the consequences?

no penalty for being negative!

consequences?

or put another way.....



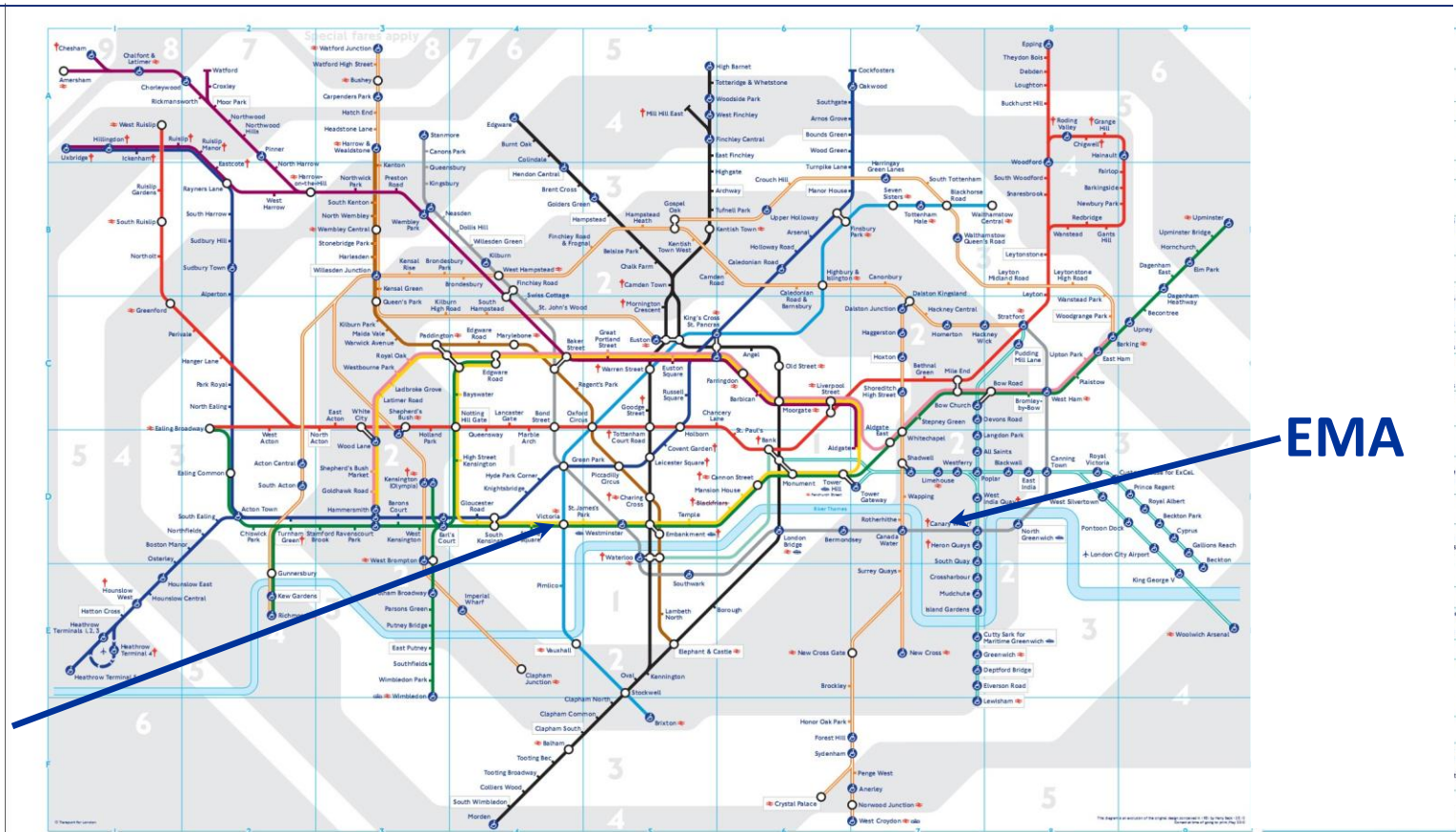
**“C’mon, c’mon — it’s either one or the other.”**

**Enough of my problems....**

**Let's turn to yours 😊**

# Regulatory Guidelines





MHRA

EMA

MAYOR OF LONDON

Website [tfl.gov.uk](http://tfl.gov.uk)

24 hour travel information [020 7222 1234](tel:02072221234)

Transport for London





**MHRA**

Regulatory guidelines are like the modern map of the London Underground.

They don't completely represent the "real" world.

There's almost always more than one way to reach an objective and the recommended route might not be the one you should follow!

The English author and moralist Samuel Johnson once said  
**“Patriotism is the last refuge of the scoundrel.”**

**I say “Rigorously following Regulatory Guidelines is the last  
refuge of those who don’t know how to develop medicines!!.”**

**NEVER FOLLOW A REGULATORY GUIDELINE IF THERE IS A  
GOOD SCIENTIFIC RATIONALE NOT TO!!!**

- General points:
  - Guidelines are generally written in order to provide an element of flexibility and not to place undue legislative restraints on scientific progress.
  - All studies should be conducted according to acceptable current protocols. Each study should be planned and designed taking into account the properties and indications of the drug concerned.
  - Requirements of OECD GLP guidelines should be met.

June 2009  
CPMP/ICH/286/95

**ICH Topic M 3 (R2)  
Non-Clinical Safety Studies for the Conduct of  
Human Clinical Trials and Marketing Authorization for Pharmaceuticals**

**Step 4**

**NOTE FOR GUIDANCE ON NON-CLINICAL SAFETY STUDIES FOR THE CONDUCT  
OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR  
PHARMACEUTICALS  
(CPMP/ICH/286/95)**

**ICH Topic S 6  
Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals**

**Step 5**

**NOTE FOR GUIDANCE ON  
PRECLINICAL SAFETY EVALUATION OF BIOTECHNOLOGY-DERIVED  
PHARMACEUTICALS  
(CPMP/ICH/302/95)**

TRANSMISSION TO CPMP	November 1996
TRANSMISSION TO INTERESTED PARTIES	November 1996
COMMENTS REQUESTED BEFORE	May 1997
FINAL APPROVAL BY CPMP	September 1997
DATE FOR COMING INTO OPERATION	March 1998

## ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals

### Step 5

<b>Part II (Addendum)</b>	
Transmission to CHMP	November 2009
Release for consultation	November 2009
Deadline for comments	February 2010
Final approval by CHMP	July 2011
Date for coming into operation	December 2011

The addendum should be read in close conjunction with the original ICH S6 Guideline.

In general the addendum is complementary to the guideline, and where the addendum differs from the original guideline, **the guidance in the addendum prevails.**

# **GOALS OF NON-CLINICAL STUDIES**

The development of a new medicinal product is a stepwise process involving an evaluation of both animal and human efficacy and safety information.

The nonclinical safety evaluation, although usually limited at the beginning of clinical development, should be adequate to characterise potential adverse effects that might occur under the conditions of the clinical trial to be supported.

## General Goals of Non-Clinical Studies

Provide an understanding of the mechanism of action

Identification of potential target organs

Characterisation of toxic effects with respect to target organs

Dose response relations

Relationship to duration and extent of systemic exposure

Potential reversibility of toxic effects

Identification of parameters for clinical monitoring (for human medicines)

Estimation of safe starting dose for clinical trials (for human medicines)

The appropriate non-clinical studies are the basis of extrapolation to indicate possible risks to humans

These studies are a means to an end, not an end in themselves

## ICH M3 (R2) allows for flexibility in approach

- Nonclinical safety studies and human clinical trials should be planned and designed to represent an approach that is scientifically and ethically appropriate.
- Pharmaceuticals under development for indications in life-threatening or serious diseases (e.g., advanced cancer, resistant human immunodeficiency virus (HIV) infection, and congenital enzyme deficiency disease) without current effective therapy also warrant a case-by-case approach to both toxicological evaluation and clinical development in order to optimize and expedite drug development.
- In these cases and for products using innovative therapeutic modalities ..., particular studies can be abbreviated, deferred, omitted, or added.

## Applying flexibility

- Patients and parents of children with rare diseases request increased access to investigational products, sometimes prior to conduct of the minimum nonclinical studies to assess safety
- Sponsors express desire for greater flexibility at times
- The MHRA CTU applies some flexibility in nonclinical requirements for rare disease products, including those to treat inborn errors of metabolism such as enzyme replacement therapies (ERTs).
- The degree of flexibility for a given program is usually based on discussions with the Sponsor, but ultimately is the non-clinical assessor's decision.

The Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals (ICH S9 Guideline) is an excellent example of flexibility being built into a guideline that is relevant to the disease in question.

November 2009  
EMA/CHMP/ICH/646107/2008

**ICH Topic S9  
Nonclinical Evaluation for Anticancer Pharmaceuticals**

**Step 4**

**NOTE FOR GUIDANCE ON  
NONCLINICAL EVALUATION FOR ANTICANCER PHARMACEUTICALS  
(EMA/CHMP/ICH/646107/2008)**

TRANSMISSION TO CHMP	December 2008
TRANSMISSION TO INTERESTED PARTIES	December 2008
DEADLINE FOR COMMENTS	March 2009
FINAL APPROVAL BY CHMP	November 2009
DATE FOR COMING INTO OPERATION	May 2010

I believe that the “principles” in ICH S9 can be applied to other diseases, especially rare diseases.

Under ICH S9, 28 day repeat-dose toxicology studies (rodent and non-rodent) can be used to support single through continuous clinical dosing, if the patient benefits, and MHRA have applied this principle to other rare or life threatening diseases where halting a clinical trial on the lack of non-clinical studies of sufficient duration would be deemed unethical.

Under ICH S9, there is no need to identify a NOAEL or NOEL in non-clinical studies. However, this is largely because usually the drugs are very toxic.

For drugs for rare diseases, I believe there is no need to identify MTD or MFD.

## Additional considerations

### Animal models of disease:

- Typically used to characterise pharmacodynamic (PD) action of drug
- Potential to supplement or replace traditional toxicity study

### Good Laboratory Practice (GLP) Studies

- Particular case specifics may preclude conduct according to GLPs
- Data can still be supportive of safety assessment

### Juvenile animal studies

- Clinical programs often initiate in paediatric populations
- Supporting safety data in a juvenile animal model is usually expected

From a safety perspective, rarity of disease generally does not influence the types of safety studies to be performed

Risk vs benefit is the primary consideration

- Benefit is not well characterised prior to Phase III trials
- Probability of benefit may outweigh safety concerns for serious and life-threatening diseases
  
- All safeguards designed to ensure safety of clinical testing still apply to drugs for rare diseases.
- These include the review of animal studies prior to initial human testing.

# **Problem Areas and How to Resolve Them**

# Scientific Advice!!

Risk comes from not knowing what you're doing!

Warren Buffett

The MHRA has, for many years, provided scientific and regulatory advice to sponsors.

Scientific advice can be requested during any stage of the initial development of the medicinal product (before submission of a marketing authorisation application), and also during the pre-submission period for a variation to an existing marketing authorisation.

Meetings can also be held with the MHRA to discuss pharmacovigilance, advertising, proposal changes to labelling or package leaflets or post-authorisations regulatory advice relating to a product range.

The MHRA prefers to meet face-to-face with companies but in exceptional circumstances, video-conferencing may be arranged.

Telephone and tele-conference meetings are generally not considered satisfactory to discuss complex scientific and regulatory issues.

The MHRA Licensing Division held about 400 Scientific Advice meetings with Companies in 2014.

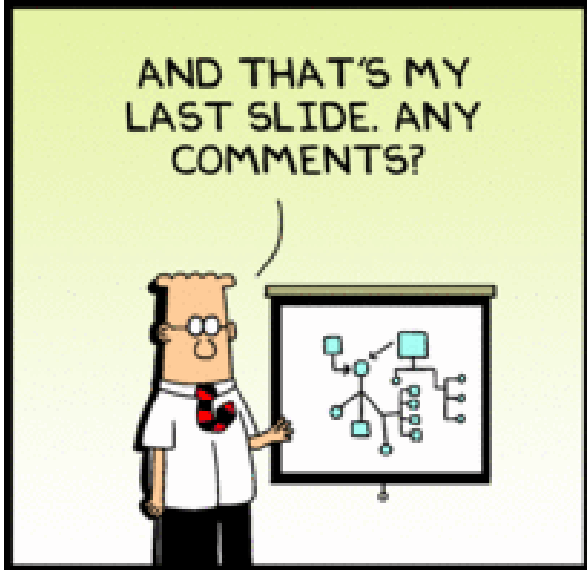
The MHRA Clinical Trials Unit has held almost 110 meetings with companies, academic institutes or hospital groups over the last 12 months!

The CTU's email helpline also fields about 250 queries a month.

Scientific advice can also be obtained from the CHMP.

The Scientific Advice Working Party (SAWP) has been established as a standing working party with the sole remit of providing Scientific Advice and Protocol Assistance to applicants.

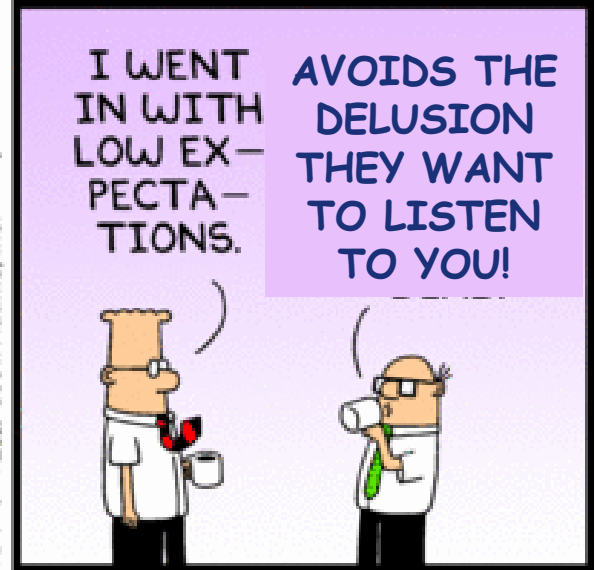
It is the SAWP/CHMP responsibility to give Scientific Advice to industry by answering to questions based on the documentation provided by the company in the light of the current scientific knowledge.



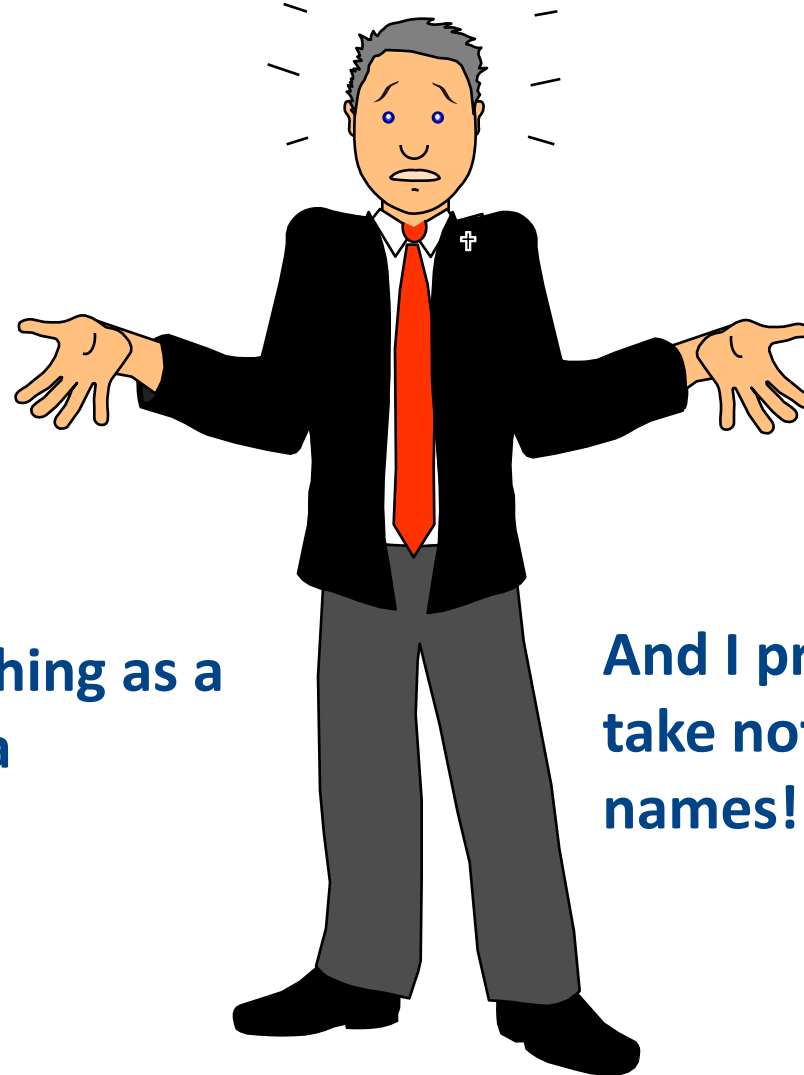
Dilbert.com DilbertCartoonist@gmail.com



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# Any Questions ?



**Don't be shy!**

**There's no such thing as a  
silly question to a  
Regulator!**

**And I promise I won't  
take note of your  
names!!**

## Any Further Questions ?

Please Feel Free to Contact the MHRA If You Have Any Further Queries:

Telephone: 020 3080 6000

Address: 151 Buckingham Palace Road  
London SW1W 9SZ

Home Page: [www.mhra.gov.uk](http://www.mhra.gov.uk)

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