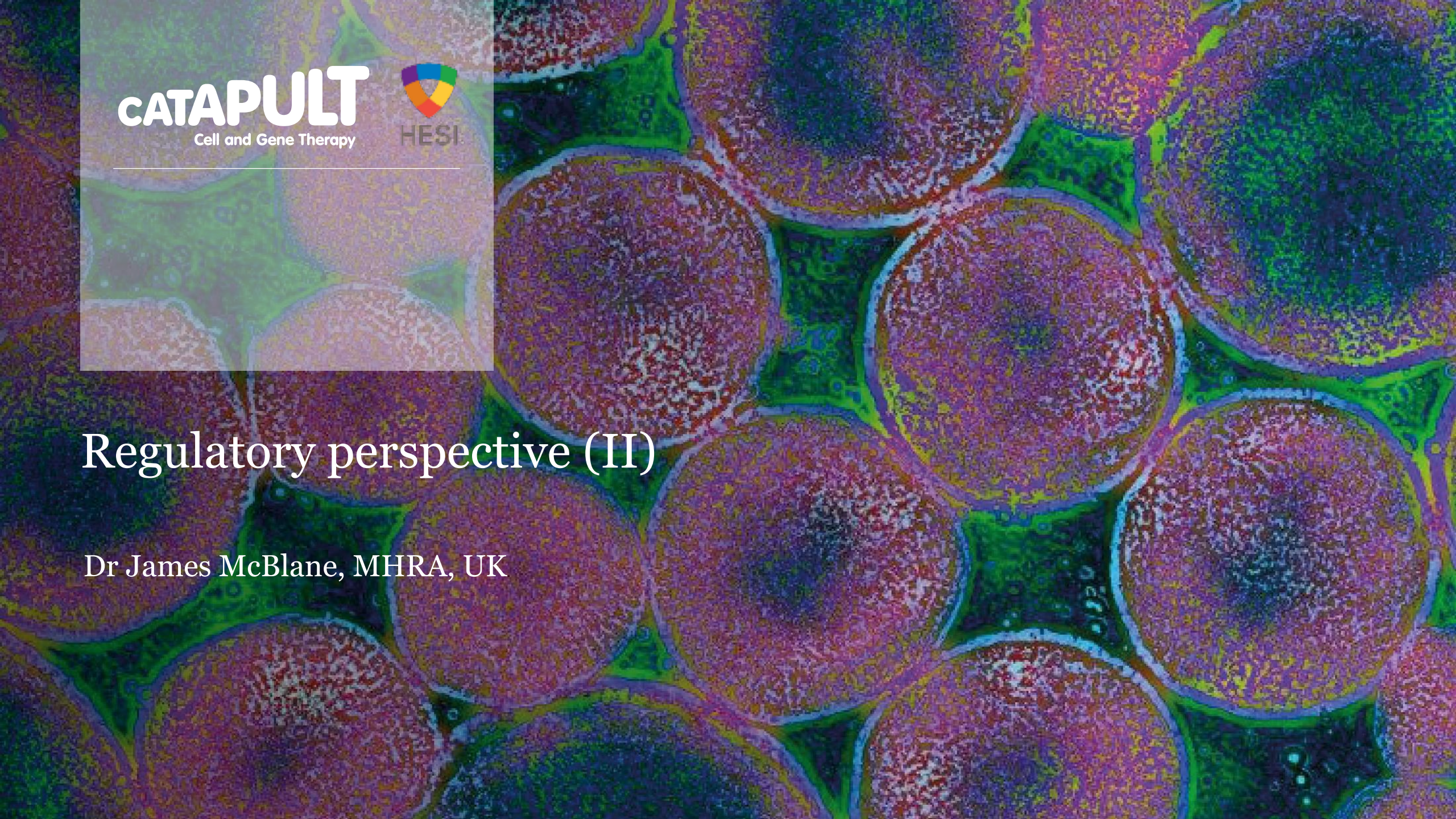

Regulatory perspective (II)

Dr James McBlane, MHRA, UK

Medicines & Healthcare products Regulatory Agency

Safety assessment of cell therapy products

CGT/CT TRACS Workshop

.JW McBlane PhD 14 February 2018

Catapult London

CPRD NIBSC MHRA

Medicines & Healthcare products Regulatory Agency

Challenges, gaps and needs to assess the safety of cell therapy products

CPRD NIBSC MHRA

Disclaimer

Opinions expressed in this presentation are my own, are not necessarily shared by other assessors at MHRA and can not be considered to be MHRA policy.

Similarly, they are not necessarily views of the Committee for Advanced Therapies (CAT), the Scientific Advice Working Party (SAWP) or the European Medicines Agency (EMA).

Background

One problem:

- I think it is still true that no patient has been dosed in the UK with a new ATMP provided on a commercial basis, despite ATMP legislation introduced in 2007 and in force from 2009

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- dreadful, but why?

- to the extent that hurdles in the preclinical dataset cause this, how can this be addressed?

JW McBlane PhD

- Origin: frae near Glasgow
- PhD pharmacologist
  - interested in the question whit does the drug dae?
  - (how) does it make the patient go away?
- In my day-to-day job I …
  - assess applications for new biological medicinal products
  - give scientific advice on biological product development
  - & since 2013, I have been the UK's alternate delegate to the European Medicines Agency (EMA)'s Committee for Advanced Therapies (CAT)
  - since January: CAT's alternate delegate to the Scientific Advice Working Party (SAWP)

Cell therapies, if medicinal products, require centralised authorisation …..

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

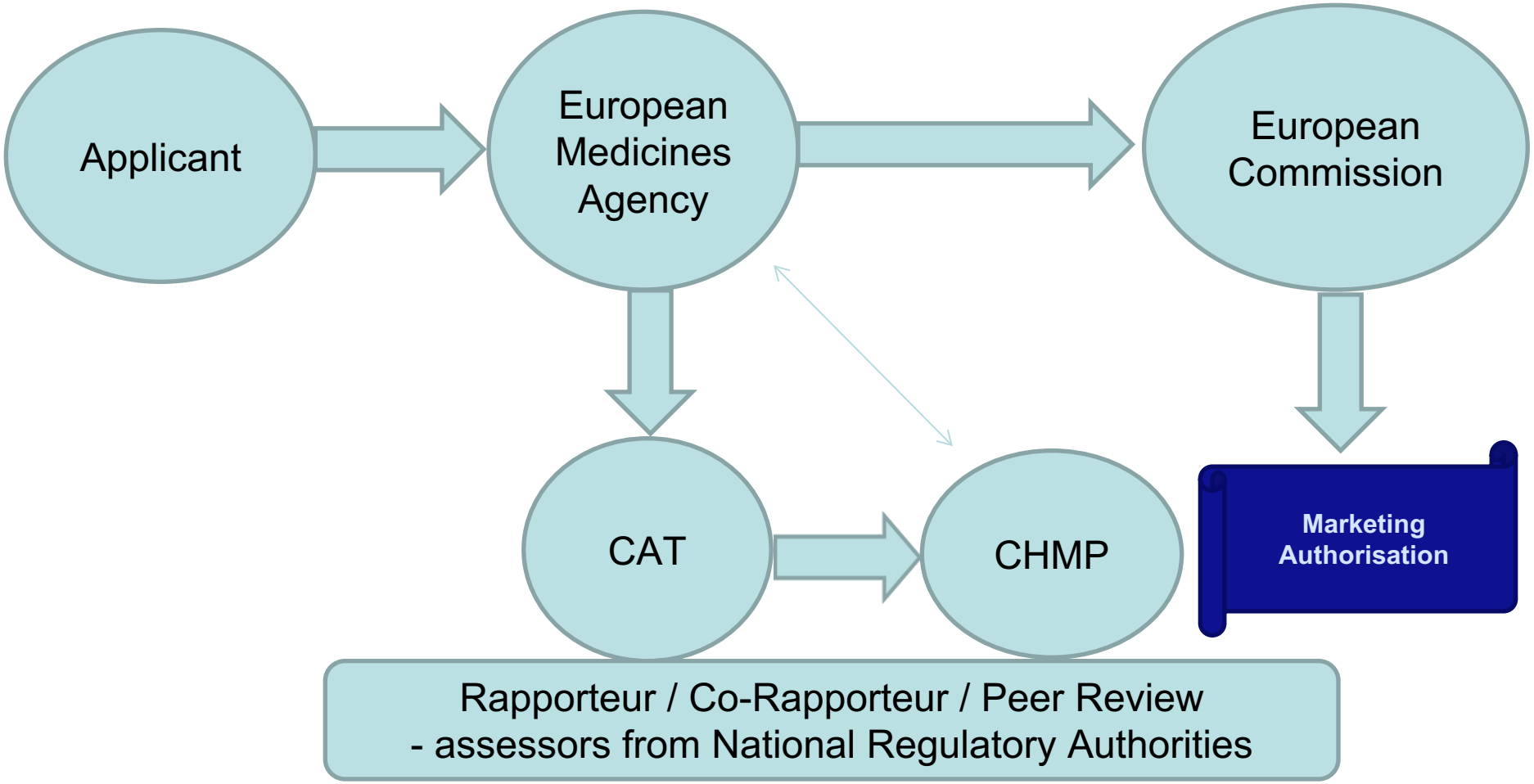
Medicines: authorisation nationally, whole EU/EEA or number of countries

European Medicines Agency (EMA)

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

MHRA not in the European Union

Regulation 1394/2007



ATMP approvals

- 9 approved (3 x GTMPs, 2 x CTMP, 4 x TEPs)

  - Glybera (AAV) - withdrawn
  - Imlygic (HSV-1)
  - Strimvelis (retrovirally transduced, autologous CD34+)
  - Zalmoxis (GM allogeneic T cells)
  - Provenge (activated, autologous PBMCs) - withdrawn
  - ChondroCelect (autologous cartilage) - withdrawn
  - MACI (autologous chondrocytes) - suspended
  - Holoclar (autologous corneal epithelial & stem cells)
  - Spherox (spheroids of autologous chondrocytes)

  + 1 Alifosel (allogeneic MSC from adipose tissue) (Dec 2017)

How to go from having products approved to having products used?

Regulation 1394/2007

Whereas …

(23) As science evolves very rapidly in this field, undertakings developing advanced therapy medicinal products should be enabled to request **scientific advice** from the Agency, including advice on post-authorisation activities. As an incentive, the fee for that scientific advice should be kept at a minimal level for small and medium-sized enterprises, and should also be reduced for other applicants.

Regulation 1394/2007

- personally, I used to believe that if a regulator gave scientific advice and the applicant followed it, it was then difficult for that same regulator to object to what was done

  ie this impedes regulators' independence

- but, one consequence – 0 (UK) patients dosed

Scientific advice

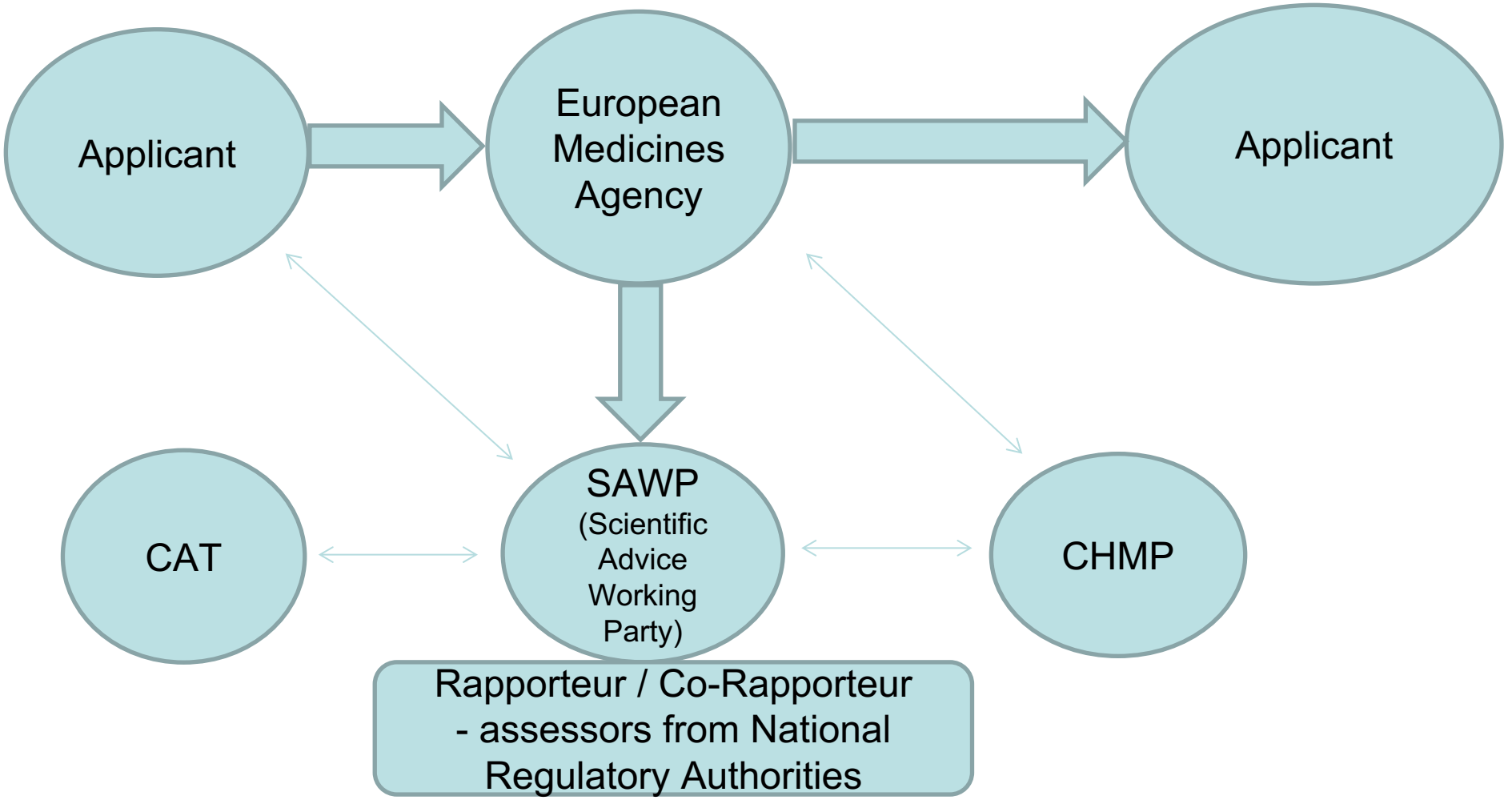
- the rest of this presentation is on

  1 the means of getting scientific advice

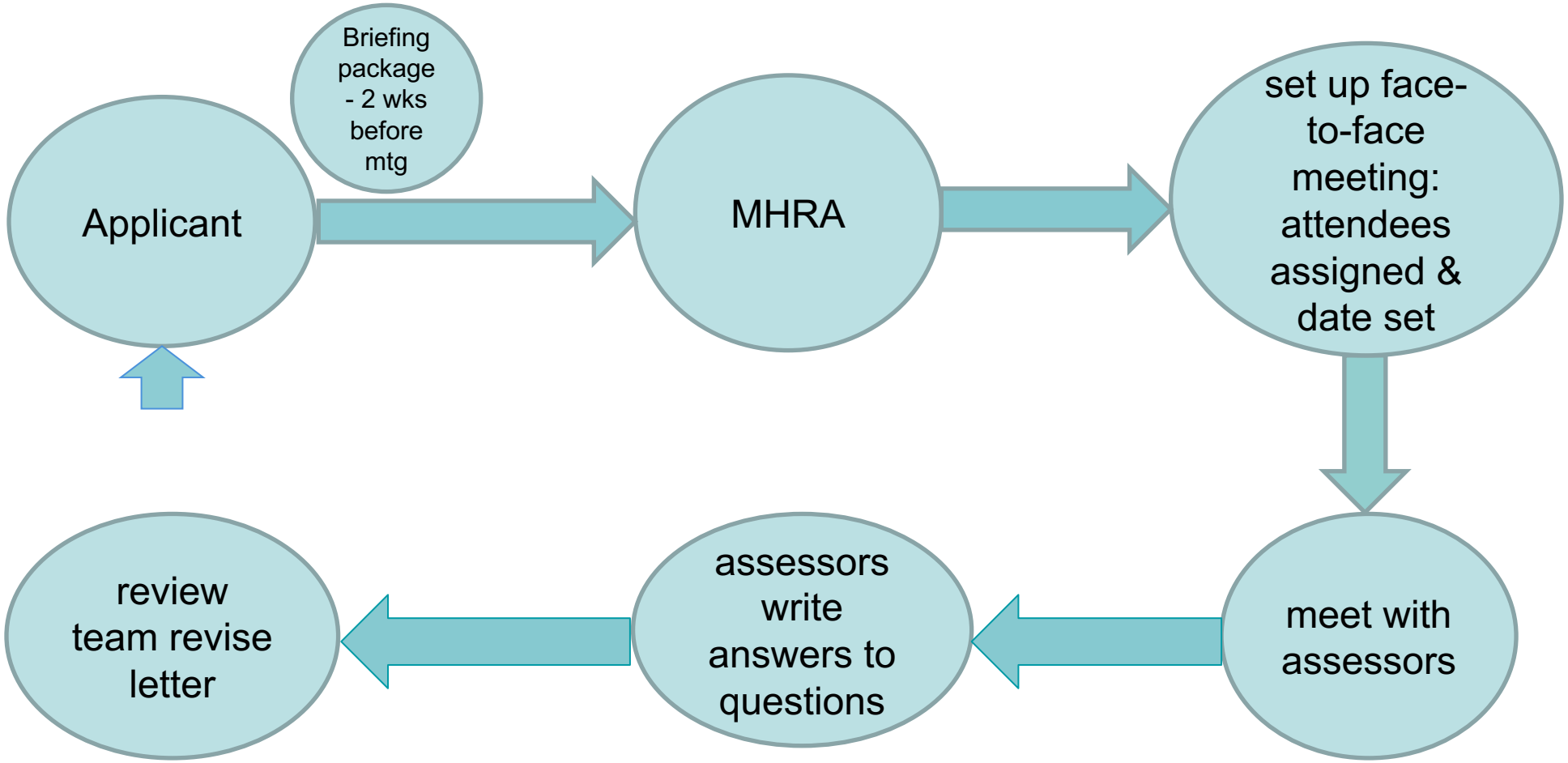
  and

  2 examples of preclinical scientific advice related to safety assessment of cell therapies

CHMP Scientific advice - ATMP: process



National advice process (MHRA)



Who is advising whom?

- companies advising regulators on what they are doing

  or

- regulators advising companies on how to get an approval

‘I had the impression they weren’t listening’

‘They were not very willing to listen to us’

so, what can you get advice on?

- or
- how to make best use of the scientific advice processes

For cell therapies …….

- In some cases, safety endpoints can be assessed in non-GLP proof of principle studies

Cavagnarro & Silva Lima Eur J Pharmacol 2015; 759: 51-62

Regulatory acceptance of animal models of disease to support clinical trials of medicines and advanced therapy medicinal products

‘ … regulatory authorities are becoming more willing to accept and even recommend data from experimental animal disease models that combine efficacy and safety to support clinical development’

For cell therapies …….

- use of veterinary experience can form the primary pharmacodynamic dataset

- imagine:
  - population of dogs with a recognised visual impairment
  - data on dogs treated with an experimental ‘dog’ medicine
  - reconstitution of biochemical and electroretinographic normality

  - injection under anaesthesia
  - longer term follow up as pets

- for other products, use of data from racehorses has also been presented

In such instances …….

- the key point is to establish how this experience is relevant to the clinical use intended
- it can cover both proof of principle and safety assessment, but maybe typically, additional studies will be done for safety assessments
- and how requiring further studies in animals prior to human use (at least for some objectives) is not necessary

For cell therapies …….

- in most cases, interest lies in understanding what cells do, where they go, for how long they last and whether they have potential for tumour formation

- typical preclinical safety dataset might be *FOR EXAMPLE*:

For cell therapies …….

- in most cases, interest lies in understanding what cells do, where they go, for how long they last and whether they have potential for tumour formation

- typical preclinical safety dataset might be *FOR EXAMPLE*:

- short term biodistribution in immunodeficient mice - human product; human route; max feasible dose: track human DNA

- general toxicity in immunodeficient mice with human product

- safety data from primary pharmacology studies - immunocompetent species (eg goat, pig) – on immunosuppressive drugs (?); human or animal cells (?)

Examples

- these are from real scientific advice questions
- but to respect privacy of applicant's data, details have been changed / deleted / made up …
- what do people actually ask?

Example 1

Question 3 – Is the non-clinical development plan adequate and sufficient to support a MAA

Example 1

Question 3 – Is the non-clinical development plan adequate and sufficient to support a MAA

- in response to this question, essentially, a full assessment of all data, including data not yet generated, needs to be completed

- scientific advice / regulatory advice / presubmission assessment?

Example 2

Does the Agency agree that there is no requirement to perform additional nonclinical studies to support marketing authorisation?

Example 3

Does the CHMP agree that our preclinical proof of concept, rationale for dose and selected doses are appropriate for the clinical development of the product?

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clinical trials are a national competency

- CHMP & EMA are not involved in reviewing CTs
- as a CT reviewer at MHRA, I did not look at CHMP advice until after I had made my conclusions on a UK CT application

Example 4

Question 11

We intend to conduct a biodistribution study, for the support of repeated doses of xx. Does the CHMP agree that the proposed design of the study is acceptable in order to complete the non-clinical evidence requirements for MAA?

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We intend to conduct a biodistribution study, for the support of repeated doses of xx. Does the CHMP agree that the proposed design of the study is acceptable in order to complete the non-clinical evidence requirements for MAA?

- athymic rats; human route of administration (not systemic); dose was ~10-fold higher than proposed in PIII; detail of readouts and timeplans provided

Example 5

Question 3

Does the Agency agree that the biodistribution study presented with the forerunner product, xxx, given by the same route as intended clinically (ie intracardiac) is sufficient to characterise what is expected for the clinical product and so no further biodistribution studies are needed to support an eventual MAA?

Significance of advice from CHMP

- ***As an assessor, in my report I can write (eg)***

- *'The applicant sought advice from CHMP in 2015 and 2017 and the final position was that CHMP advised that no in vivo tumourigenicity study is required for xx. The applicant should summarise published data with xx and show how such data are relevant to xx. The applicant ha provided a suitable discussion as summarised below.'*

- if I have a different view, it's then up to me to convince CHMP to revise their position

Also …..

- Beyond scientific advice there are further mechanisms to help you develop your product

- How?
  - ITF – Innovation task force
  - PRIME – Priority Medicines initiative
  - EAMS (UK) – Early Access to Medicines Scheme
  - Innovation Office – early advice from MHRA
  - Classification - by CAT at EMA
  - Certification – by CAT at EMA – might this help?

In summary, if developing an ATMP, I would ….

AT THE BEGINNING:

is this product an ATMP?

- (if necessary) seek classification by CAT (at EMA)

EARLY IN DEVELOPMENT:

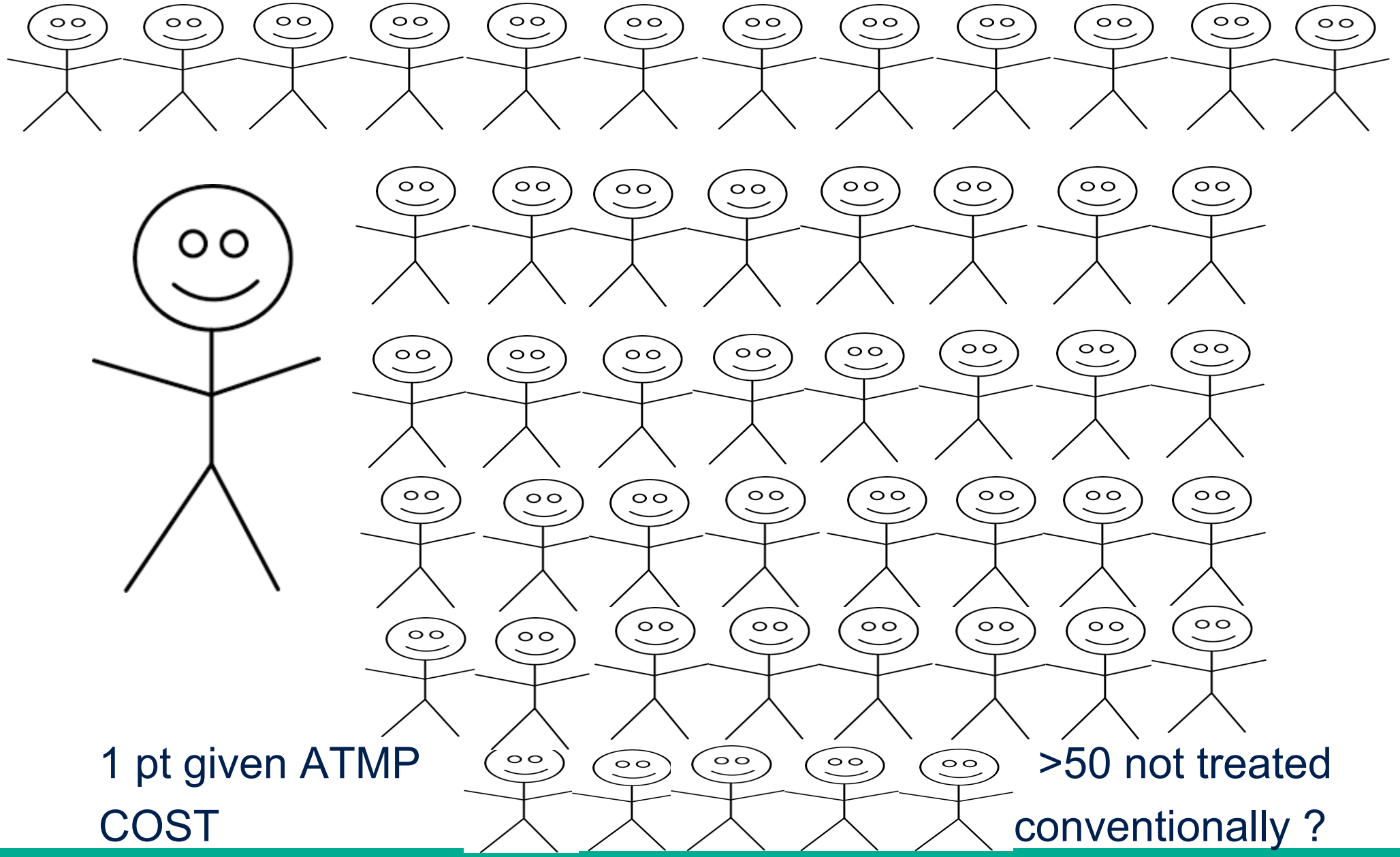
can we do this as the 1st trial with this as the product?

- meet national authority of country/ies where you plan the trial

WITH INITIAL CLINICAL RESULTS:

do CHMP agree with current data and plans for future manufacturing changes and plans for preclinical & clinical data for an MAA?

- formal EMA SAWP scientific advice (with FDA too ….)



1 pt given ATMP

COST

>50 not treated

conventionally ?

Thank you for listening

Any questions?

Contact details

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UK

But, note MHRA will move to Canary Wharf later in 2018

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