

**Report of the *Expert Group on  
innovation in the regulation of  
healthcare***

25 September 2013

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# 1. Introduction

- 1.1. The *Expert Group on innovation in the regulation of healthcare* was established in June 2012 following the Prime Minister's 2011 Life Sciences Strategy.<sup>1</sup> Following a year of discussions and constructive engagement, this report to Ministers in the Department of Health (DH) and Department for Business Innovation and Skills (BIS) fulfils the commitment in the strategy for a task and finish group to conclude and report to ministers in September 2013:

*A group of experts drawn from government, regulators, the NHS, industry and the academic and third sector communities will meet quarterly to discuss healthcare regulation issues, including the development of new initiatives and innovations... This will set out measures of performance such as the use of conditional authorisation pathways, and uptake of the Early Access Scheme, alongside 'next steps' proposals for further regulatory innovation.*

- 1.2. The group was established to respond to claims highlighted in the Life Sciences Strategy that the licensing process was long and expensive. There was demand from patient groups for earlier access and calls from industry that there was economic impact of a development pipeline typically lasting several years and costing hundreds of millions of pounds. This was a problem in particular for Small and Medium Sized Enterprises (SMEs) who find it hard to fund Phase III research, and are less well-placed to bear the cost of a long development process from discovery to market. It was also problematic for medicine development in general as the sector increasingly develops medicines for stratified patient groups and rarer diseases. There was also concern that European conditional authorisation and schemes for accelerated assessment of products might be used less frequently than their equivalents operated by the Food and Drugs Administration (FDA) in the United States, and reasons for this should be explored.
- 1.3. The group was chaired by the Medicines and Healthcare Products Regulatory Agency (MHRA) Chief Executive Sir Kent Woods and membership was drawn from government, regulators, the NHS, industry, and the academic and third sector communities. The findings from the group's discussions are presented in this report, along with a more detailed summary of the group's discussions at its six meetings and information on the composition of the group.

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<sup>1</sup> [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf) page 29

- 1.4. Findings are presented on the following topics:
- Early Access to Medicines Scheme
  - Adaptive licensing
  - Regulatory incentives and flexibilities
  - International perspectives – including EU/USA comparison and breakthrough designation
  - Advanced manufacturing
  - Supporting the wider innovation agenda including
    - Clinical Practice Research Datalink (CPRD)
    - Clinical Trials
    - The new pharmacovigilance (PV) legislation.

25 September 2013

## 2. Summary of conclusions and recommendations

- 2.1. The Expert Group on innovation in the regulation of healthcare was established in June 2012 following the Prime Minister's 2011 Life Sciences Strategy.<sup>2</sup> This report to DH and BIS Ministers fulfils the commitment in the strategy for a task and finish group to conclude and report to ministers in September 2013 on regulatory innovation.
- 2.2. Initial discussions of the Expert Group were about how to accelerate patient access to medicines, both unlicensed and licensed, and also how to explore flexibilities in the regulatory regime. To tackle issues relating to unlicensed medicines, the UK Government has consulted on an Early Access to Medicines Scheme for highly promising unlicensed medicines in areas of high unmet medical need (see Annex v). In relation to more efficient licensing, the group considered the concept of adaptive licensing as defined by the European Medicines Agency (EMA). This relates to a more proactive use of existing flexibilities<sup>3</sup> in European law rather than requiring new or revised legislation. The aim would be to enable a licence to be granted earlier in the drug development pipeline with the appropriate safe guards in place. Both these schemes are at critical stages in development.

### **Early Access to Medicines scheme**

- 2.3. On Early Access, the group welcomed the proposal for a UK Early Access scheme, operating within European rules for unlicensed medicines, for highly promising unlicensed medicinal products in areas of high unmet medical need, at a stage in their development where they are nonetheless deemed to be sufficiently safe and efficacious in the context of the high degree of need and absence of appropriately safe and effective alternatives. The group considered and endorsed the draft Government response to the consultation at its April meeting, pending the conclusion of discussions with Government on funding aspects of the scheme. The group recognised the inevitable uncertainty in both the benefits and risks associated with medicines used in this way and MHRA must ensure that robust processes to reduce uncertainty and ensure safety are an integral part of the scheme.

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<sup>2</sup> [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf) page 29

<sup>3</sup> Regulatory incentives (such as market and data exclusivity) and flexibilities (approval with conditions, conditional approval, exceptional circumstances and accelerated assessment). More information is in Annex ii

### **Recommendation 1**

***The Expert Group is supportive of the Government launching an Early Access to Medicines Scheme as soon as possible and urged the Government to conclude discussions on the funding aspects of the scheme.***

#### **Adaptive licensing**

- 2.4. The Expert Group considered that in relation to quality, safety and efficacy aspects, the concept of adaptive licensing would need to relate to a more proactive use of existing flexibilities in European law, such as the flexibility to license conditionally as defined by the EMA.<sup>4</sup> The development of new or revised legislation requires a lengthy process. Wider system changes such as to Health Technology Assessment (HTA) processes or data capture were not within the remit of the Expert Group.
- 2.5. This year the EMA will, subject to final agreement, publish a number of retrospective case studies for adaptive licensing along with guidance and a call for live assets (products) to go through the process. The Expert Group noted that UK-based companies have been reluctant to come forward with specific pilot products for adaptive licensing until the details of the EMA's proposals are made clearer. When they are able to do so, areas that are Government priority areas for action such as anti-microbials or rare or debilitating diseases where there is unmet medical need might be suitable candidates.
- 2.6. The Expert Group welcomed the European developments and welcomed MHRA's continued commitment to support innovation. The MHRA currently does this through scientific advice to companies - it currently holds over 250 meetings per year nationally, and also fully participates in European scientific advice. In addition, support for innovation is facilitated by being clear as to the expectation for licensing (via guidance, including communicating on legal flexibilities available), by ensuring an appropriately balanced approach is taken to risk benefit, ensuring that regulatory flexibilities are used and by participating actively in the development of the adaptive licensing approach at EU level.

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<sup>4</sup> Adaptive Licensing is defined as "a prospectively planned, adaptive approach to regulation of drugs. Through iterative phases of evidence gathering, followed by regulatory evaluation and license adaptation, adaptive licensing seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to provide adequate evolving information on benefits and harms."

- 2.7. The Group noted, and welcomed, the work that the MHRA had done in this respect so far and urged it to continue with its proactive engagement. It is encouraging that the UK continues to assess more centralised medicines than any other Member State. The group also welcomed the establishment during the year of the Centre for the Advancement of Sustainable Medical Innovation (CASMI) and its support for the wider aspects of adaptive licensing.

### **Recommendation 2**

**The group tasked the MHRA, which is actively involved in development of adaptive licensing, to press for available legal flexibilities to be used to facilitate innovative products to reach patients. The EMA should be pressed to launch a call for adaptive licensing at the earliest opportunity so that companies could put forward pilot products.**

### **Regulatory incentives and flexibilities**

- 2.8. The group noted that there were already a number of regulatory incentives (such as market and data exclusivity, orphan drug designation) and flexibilities (approval with conditions, conditional approval, exceptional circumstances and accelerated assessment) within the EU framework that were used by companies to gain approval more quickly.
- 2.9. The Expert Group noted examples of where genuine breakthrough products, such as Kalydeco (Ivacaftor), had rapidly proceeded through the regulatory system.<sup>5</sup> The Expert Group noted the lack of research evidence that quality, safety and efficacy regulation is slowing down innovation or somehow preventing breakthrough products, even for small patient populations, from getting marketing authorisations. At the time of consideration by the group in April and July 2013, there were 12 active conditional approvals in the EU and 25 licensed under exceptional circumstances.<sup>6</sup>
- 2.10. Industry bodies told the Expert Group that there was less awareness of these flexibilities among all UK companies that was commonly assumed, so it was encouraged that MHRA responded by the prompt

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<sup>5</sup>Kalydeco (Ivacaftor) is an orphan product that was granted (approved) with conditions. It is licensed for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have a *G551D* mutation in the *CFTR* gene. Accelerated Assessment procedure was agreed-upon by CHMP. Procedure started on 16 November 2011, positive opinion issued by CHMP 24 May 2012 with an obligation on the applicant of an observational study and final study report of extension study evaluating long term safety.

<sup>6</sup> See lists on pp 32-33 in Annex ii

publication of information about them.<sup>7</sup> The group welcomed the establishment of the MHRA Innovation Office in March 2013 and the benefit of this straightforward single point of contact for industry and other interested stakeholders. It was recognised that innovative products or technologies are often developed by academics or SMEs who have little or no regulatory affairs expertise. However, the Expert Group considered more could be done to communicate flexibilities to industry. Early engagement between regulators and companies would continue to be key if perceived barriers to innovation are to be overcome.

- 2.11. The MHRA and the National Institute for Health and Care Excellence (NICE) set up a pilot system in March 2010 for joint advice meetings with companies. This would result in parallel advice from MHRA on medicines licensing issues and NICE on HTA issues. It would facilitate discussions at an earlier stage on HTA aspects and there were similar initiatives at European level and in other European Member States. However there had only been one joint NICE/MHRA meeting requested and reasons for low uptake were not known. MHRA and NICE proposed to re-launch and rejuvenate this scheme at the time of the Expert Group report in September and this was welcomed by the group. The scheme should consider involving the devolved HTA bodies in the rest of the UK.

**Recommendation 3**

**MHRA should launch a communications programme in September 2013 to highlight the existing licensing flexibilities to encourage proactive consideration of their use by companies at earlier stages in the product development process.**

**Recommendation 4**

**MHRA/NICE should re-launch joint NICE/MHRA advice meetings to increase uptake so that companies can consider medicines regulation and Health Technology Assessment (HTA) issues in parallel and consider involving HTA bodies in devolved administrations.**

**International comparisons**

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<sup>7</sup><http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Regulatoryschemesthatsupportdrugdevelopmentlicensingandpatientaccesstoinnovativetherapies/index.htm>

- 2.12. The group welcomed MHRA participation in international discussions on regulatory innovations, especially the US MIT-led NEWDIGS initiative. It was noted that work under the NEWDIGS initiative had brought together global regulators and leaders on adaptive licensing and similar issues were surfacing at international level that arose in UK discussion, especially the need for pilot products to go through the system. The group also noted the links being made by NEWDIGS to the Innovative Medicines (IMI) initiative in Europe and the work led by the European Federation of Pharmaceutical Industries and Associations (EFPIA) on medicines adaptive pathways to patients (MAPPs).
- 2.13. The group went on to consider the flexibilities available in the USA and EU and noted that the two regulatory systems offered substantively similar flexibilities.<sup>8</sup> However, the one substantive difference was the US's 2012 "breakthrough therapy" designation<sup>9</sup> that gave strong signals to investors on promising products. It will be important to continue monitoring the progress of medicines designated by the US FDA as breakthrough therapies through the USA and EU regulatory frameworks.

**Recommendation 5**

***The Expert Group recommended that the Government consider the possibility of adopting a designation that would send signals to investors (as does the US breakthrough designation), perhaps in the context of the proposed UK Early Access scheme. The MHRA should also press for the EU to consider a similar approach at EU level, bearing in mind the need to progress quickly on this agenda given the apparent early success of the US designation.***

**Advanced manufacturing**

- 2.14. On advanced manufacturing, the Expert Group noted that there was scope in the current regulatory framework to permit advanced manufacturing and MHRA had established mechanisms for early engagement with organisations involved. It was encouraging that it was mainly SMEs who came forward for advice.

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<sup>8</sup> A comparison table between EU and US regulatory flexibilities is at Annex iii of this report.

<sup>9</sup> <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAAct/SignificantAmendments/totheFDCAAct/FDASIA/ucm341027.htm>

- 2.15. The group noted that the BIS Focus on Enforcement pharmaceuticals theme launched in July 2013 would provide an opportunity for the sector to comment on this area, along with a project on pharmaceutical manufacture under the auspices of the Ministerial Industry Strategy group. Both of these were ongoing at the time of writing this report. The related work of the National Biologics Industry Innovation Centre (NBIIIC) was also welcomed.

**Recommendation 6**

***The Group encouraged both MHRA and organisations involved in advanced manufacturing to continue early engagement on these issues.***

**Supporting the wider innovation agenda**

- 2.16. Although the Expert Group restricted its deliberations to the medicines licensing regulatory framework within its remit, it noted that the ability to use large linked databases such as the Clinical Practice Research Datalink (CPRD) could make the UK a world leading place to monitor medicines on the market, which facilitates regulatory innovation and links to the work of wider Government and the research community to promote clinical trials in the UK. Trends in the number of clinical trials undertaken in the UK are similar to those in the rest of the EU and the Expert Group welcomed the work of MHRA in relation to the ongoing negotiation of the European Clinical Trials Regulation which would streamline processes across Europe. The group supported the use of epidemiological studies using data sources like CPRD to ensure the monitoring of the risk/benefit balance of medicines, especially introduced under adaptive licensing, protects patients and public health.

**Recommendation 7**

**The group supported MHRA work to progress clinical trials regulation negotiations and hoped they would be successfully completed as soon as possible.**

**Conclusion**

- 2.17. In conclusion, the Expert Group has found that there is an enabling medicines regulatory environment in the EU, with existing legal flexibilities to accelerate patient access to innovative medicines and that ongoing engagement must continue to ensure the EU regulatory environment maintains this enabling nature. These existing flexibilities could be exploited further by companies to foster innovation.

Regulatory developments in adaptive licensing represent an encouraging global shift in regulator and industry attitudes to risk: benefit assessment. The UK has a key role to play in pushing the innovation agenda forward in Europe through established networks and ensuring companies have access, through the MHRA, to high quality, scientific advice. Regulators should continue to recognise they have a key role in supporting innovation, and be available to advise applicants throughout the process, so that collectively important new drugs are developed optimally.

- 2.18. The next steps for this agenda will be to continue to advance the adaptive licensing agenda at an EU level, launch an Early Access to Medicines Scheme for unlicensed medicines as soon as possible, continue the work on advanced manufacturing under MISG and position the medicines regulatory framework and UK services provided by MHRA as part of the wider Government work to support innovation and work on Anti-Microbial resistance. A communications strategy should be developed to ensure that the legal flexibilities available are understood and exploited by companies and to set medicines regulation in the wider innovation landscape.

### **3. Detail of Expert Group discussions**

#### **3.1. Proposal for a UK Early Access to Medicines Scheme for unlicensed medicines**

3.1.1. As set out in the terms of reference, this was one of the priority areas for the Expert Group to consider. The group discussed this issue at every meeting.

3.1.2. As reported in the group's findings, the group welcomed the proposal for a UK Early Access to Medicines Scheme operating within European rules for unlicensed medicines to meet unmet need. The group considered and endorsed the draft Government response to the consultation at its April meeting. The group advised that it should be launched as soon as cross-Government agreement was obtained.

3.1.3. The group endorsed the proposal that in order to meet legal requirements and fill a gap in current regulatory practice, this scheme would be for medicinal products that will treat, diagnose or prevent life threatening, chronic or seriously debilitating conditions without adequate treatment options. The scheme is aimed primarily at medicines that have completed phase III trials, but may be applied to completed phase II trials in exceptional circumstances. The group recognised the inevitable uncertainty in both the benefits and risks associated with medicines used in this way and MHRA must ensure that robust processes to reduce uncertainty and ensure safety are an integral part of the scheme.

3.1.4. At the time of writing the report, discussions across Government were ongoing, including with NHS England.

3.1.5. Successful implementation of the scheme would be a good example of multi-stakeholder work joined up across the MHRA,

NHS and HTA bodies. Learnings from this process will be important in implementation of potential change relating to adaptive licensing and in facilitating future regulatory innovation.

### **3.2. Adaptive licensing**

3.2.1. This was another priority area in the group's terms of reference and again this issue was discussed at every meeting.

3.2.2. Although there is no agreed definition of adaptive licensing, the group considered that with respect to quality, safety and efficacy aspects the concept, as defined by EMA, relates to the pragmatic use of existing regulatory flexibilities. The group accepted that, the European Commission is by law the licensing authority for most innovative medicines through the centralised procedure. This gives industry access to the entire European market through a single approval process and is widely seen to reduce the burden on industry of applying in each individual member state. This means that it is necessary to have the adaptive licensing debate at EU level.

3.2.3. Although the group did not rule out further reform at EU level in the longer term, there was not sufficient evidence at this stage that a wholesale redesign of European medicines legislation was necessary to meet the aims of adaptive licensing.

3.2.4. The MHRA was tasked with developing a pilot programme for adaptive licensing that was considered by the Expert Group in January 2013. The pilot programme sets out the different strategic elements that need to come together to make adaptive licensing happen. This work is at European and national levels, and involves government, industry and the third sector. The pilot programme notes the key role of the European Commission as licensing authority.

3.2.5. The MHRA will launch a communications plan in 2013 to further communicate the current flexibilities to industry, which will enable them to respond to the forthcoming EMA publication of guidance, case studies and a call for products (“live assets”) to go through the process. MHRA is fully engaged with this work at the EMA, fully represented at all the relevant committees and working parties and will continue to do all it can to support innovative products appropriately using regulatory flexibilities and adaptive licensing. The potential role of CASMI in fostering the non-regulatory aspects of adaptive licensing was noted.

3.2.6. At the July 2013 meeting anti-microbial resistance was highlighted as a Government priority. This is an area where quick development was key and might be suitable for adaptive licensing, as are rare or debilitating diseases where there is unmet medical need.

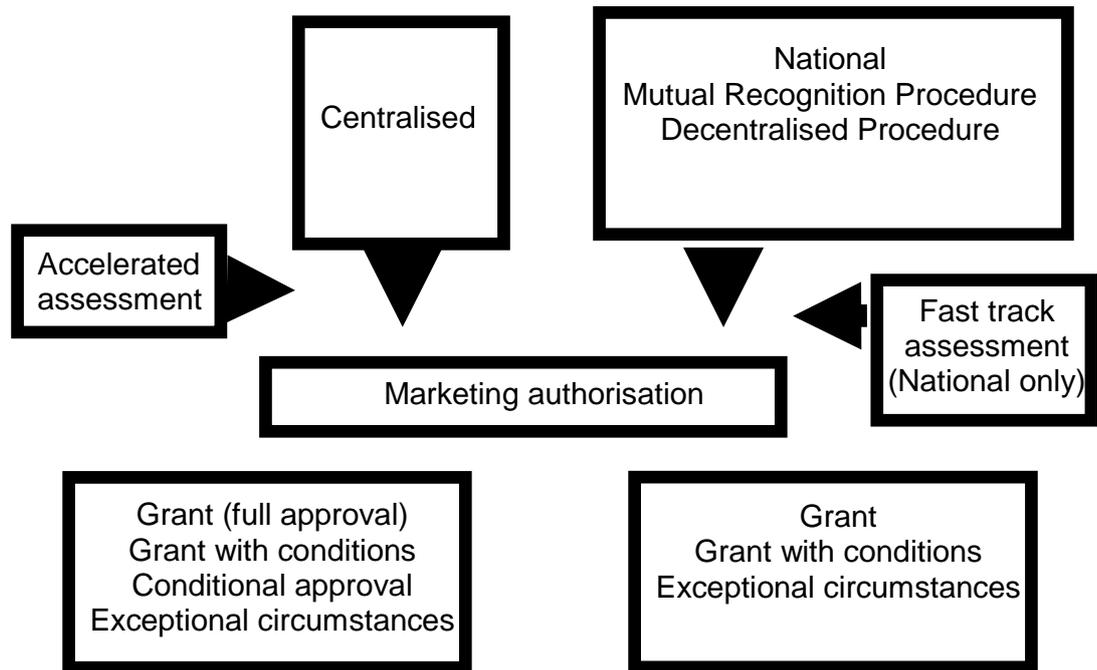
### **3.3. Regulatory incentives and flexibilities**

3.3.1. The Expert group discussed in October 2012 and April 2013 the routes to licensing in the UK (under European legislation) and the regulatory incentives and flexibilities. It was noted that the European centralised procedure is, by law, used for the majority of innovative medicines. This route includes the following flexibilities:

- Approval with conditions
- Conditional approval
- Exceptional circumstances
- Accelerated assessment

3.3.2. These are summarised in Figure 1 below.

Fig 1. Summary - drug licensing routes



3.3.3. Following the discussions of the first meeting of the group, which highlighted a lack of awareness among some smaller companies regarding the possible routes to gaining a marketing authorisation, the MHRA circulated – and put onto its website – information about flexibilities under the existing UK and EU licensing processes.<sup>10</sup>

3.3.4. The group noted that at the time of considering this issue, there were 12 active conditional approvals in the EU (licensed on less complete data package than normally required to meet unmet medical need) and 25 licensed under exceptional circumstances (licensed on a less complete data package as the applicant demonstrated that he is unable to provide comprehensive data on the safety and efficacy under normal conditions of use). This demonstrates that the flexibilities can, and are, used by some

<sup>10</sup><http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Regulatoryschemeesthatsupportdrugdevelopmentlicensingandpatientaccesstoinnovativetherapies/index.htm>

companies. A case study of a product licensed in this way is **Kalydeco (ivacaftor) in Figure 1 on the next page.**

3.3.5. The paper that the Expert Group considered in April 2013 is reproduced in full as Annex ii as it sets out the information considered by the group in detail.

## **Fig 1. CASESTUDY IN USE OF REGULATORY FLEXIBILITIES**

### **Kalydeco (ivacaftor) – Licensed with conditions using accelerated assessment in the Centralised Procedure**

#### **The product**

- Kalydeco (ivacaftor) is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the *CFTR* gene.
- Posology for Adults, adolescents and children aged 6 years and older (no data in children under 6)
- Ivacaftor is a selective potentiator of the CFTR protein, increases CFTR channel gating to enhance chloride transport (exact mechanism leading to prolong gating activity of some mutant CFTR forms has not been completely elucidated).

#### **Regulatory review**

- Kalydeco was designated as an orphan medicinal product July 2008.
- At the time of submission of the application, the Paediatric Investigation Plan (PIP) was not yet completed as some measures were deferred.
- Accelerated Assessment procedure was agreed-upon by CHMP.
- Procedure started on 16 November 2011, positive opinion issued by CHMP 24 May 2012.

#### **Obligation to complete post-authorisation measures**

- The applicant should conduct a 5-year long-term observational study including microbiological and clinical endpoints (e.g. exacerbations)
- The applicant should submit the final clinical study report of the ongoing study VX08-770-105 which evaluates the long-term safety and efficacy in patients with CF
- The applicant should submit the verification protocol for scale-up of the Design Space in case of any changes to the Normal Operating Ranges (NORs) in the manufacture of the active substance

### 3.4. International comparisons

#### 3.4.1. Breakthrough designation

3.4.1.1. Breakthrough therapy designation is a FDA initiative which came into force in July 2012 following amendment of the *Food and Drug Administration Safety and Innovation Act* (FDASIA). A frequently asked questions document<sup>11</sup> is available and describes breakthrough designation as:

*Breakthrough therapy designation is intended to expedite the development and review of drugs for serious or life-threatening conditions. The criteria for breakthrough therapy designation require preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy. A breakthrough therapy designation conveys all of the fast track program features (see below for more details on fast track designation), as well as more intensive FDA guidance on an efficient drug development program. The FDA also has an organizational commitment to involve senior management in such guidance.*

3.4.1.2. Much interest has been generated by the FDA's breakthrough designation, where promising new medicinal products are designated based on preliminary clinical evidence and are considered to have potential for 'substantial improvement on at least one clinically significant endpoint over available therapy'. The Expert Group considered the FDA's breakthrough designation in July 2013 and concluded that the EU regulatory regime, although operating in a different environment, offers similar flexibilities as the US scheme.

3.4.1.3. Breakthrough designation is one of number of ways that a product can benefit from expedited assessment or regulatory flexibilities in the USA. Annex iii provides a comparison of EU

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<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendments/totheFDCAct/FDASIA/ucm341027.htm>

and USA licensing flexibilities. The table in Annex iv provides a specific comparison of breakthrough designation with the MHRA's similar initiatives. It will be important to continue to review the progress of medicines designated by the US FDA as breakthrough therapies through the USA and EU regulatory frameworks.

### 3.4.2. ***Early Access candidate designation as part of the MHRA scientific advice process***

3.4.2.1. The MHRA has developed a proposal for a UK Early Access to Medicines scheme where the aim is to provide earlier availability of promising new medicines to patients that have a high unmet clinical need. The Early Access Scheme will cover medicines that are still being developed but cannot yet be made available as licensed treatments.

3.4.2.2. In order to assist companies with their development plans and to ensure that innovative products reach UK patients in an expedited fashion, the MHRA will offer scientific advice specifically covering the eligibility criteria of the early access scheme and the potential data requirements. This scientific advice will consist of a face-to-face meeting with experienced assessors and management and the company, and where the potential of the product and suitability of the development plan for the scheme can be discussed. Following the advice meeting, the company will receive a letter from the MHRA, detailing the discussion and confirming whether the product can be considered as being potentially eligible for the scheme. At this stage it might be possible for these products to be designated as potential candidates for Early Access.

3.4.2.3. For products that go through the scheme, the MHRA will provide a scientific opinion on new medicines that will treat, diagnose or prevent life threatening, or seriously debilitating conditions without adequate treatment options before they are formally licensed. The scientific opinion will describe the benefits and risks of the medicine and the opinion will be made available on the MHRA's website to assist clinicians and patients in making treatment decisions. Importantly, it is expected that the scheme would provide access to the medicine up to a year before the regulatory process delivers a marketing authorisation.

### **3.5. Advanced manufacturing**

3.5.1.1. The group considered this issue in July 2013. The group noted that there was scope for flexibilities in the current regulatory framework to permit advanced manufacturing and the mechanisms that MHRA had in place for early engagement with organisations involved. Sectors of industry were moving away from high capital cost plants to flexible technologies and units, so early engagement with the regulator was considered to be key.

3.5.1.2. MHRA has for some time had several mechanisms in place for the phased engagement with organisations involved in advanced manufacturing. These have been expanded and given more visibility by the establishment of the Innovation Office. It was noted that mainly SMEs came forward for advice.

3.5.1.3. The perception among some members was that there needed to be a more enabling environment for manufacture in the UK. This would not just relate to pharmaceutical regulation but the entire economic

landscape. Under the auspices of the MISG, a project was established in summer 2013 to look at the wider issues relating to manufacturing in the UK, as well as medicines regulation. The work of the National Biologics industry innovation centre (NBIIC) was welcomed. MHRA confirmed it was in discussion with NBIIC and the cell therapy and high value catapults of the Technology Strategy Board of BIS.

### **3.6. Clinical Practice Research Datalink (CPRD)**

- 3.6.1. In April 2013 the group received a presentation on the CPRD Clinical Trial software. The group noted that the ability to use large linked databases such as CPRD could make the UK a world leading place to monitor medicines on the market. This is because they can lead to pharmacovigilance (PV) activities being undertaken in a proactive, rather than reactive fashion. For example, the MHRA is now routinely looking at adverse reactions to vaccines on a rolling basis, by utilising both Yellow Card and CPRD data.
- 3.6.2. CPRD already has data from 5 million patients from primary care and in September 2013 will have hospital data integrated within the system. The IT developments will enable better trial feasibility, protocol optimisation, site/patient recruitment as well as enable other efficiencies.
- 3.6.3. The group noted that if clinical trials were conducted through CPRD, there was also the potential for longer-term electronic follow-up of trial patients, which could provide data on such an exposed cohort in a timely fashion. Linkages to other data sets, such as the Office of National Statistics mortality data could provide valuable further information.

### **3.7. Clinical Trials**

- 3.7.1. The group discussed papers on clinical trials in April and July 2013. Although the number of trials had gone down in the UK this

was now plateauing and reflected trends in other EU countries. It was noted that the UK has some particular attractiveness in niche areas such as Advanced Therapy Medicinal Products and exploratory (or early phase) clinical trials.

3.7.2. Initiatives undertaken to promote clinical trials in the UK have made use of flexibilities available in the current legislation. These initiatives broadly fall into two groups – supporting applications prior to submission and streamlining the authorisation process. The group welcomed how MHRA have responded to requests to simplify processes on clinical trials and introduce a risk-adapted approach in conduct of trials.

3.7.3. The group welcomed the work of MHRA in relation to the ongoing negotiation of the European Clinical Trials Regulation which would streamline processes across Europe. The group hoped the negotiations would be successfully completed as soon as possible.

3.7.4. The group noted and welcomed the work to promote clinical trials in the UK, noting that the regulatory aspects were one part of a much wider programme of work being co-ordinated by the Department of Health working with the National Institute for Health Research and the Health Research Authority

**3.7.5. New Pharmacovigilance (PV) legislation and the Life sciences agenda**

3.7.5.1. In July 2013 the group considered a paper on this issue. The following key points were noted:

- New legislation from July 2012 meant risks should be considered in the context of benefits with weight placed on the need to consider outcomes and the effectiveness of risk minimisation. The new legislation includes a legal basis for

PV requirements to be conditions of the Marketing Authorisation (MA).

- UK requires adverse reactions of unlicensed medicines to be reported through its specials scheme. As the proposed Early Access Scheme would be implemented under existing legislation, the same legal basis would apply for PV for Early Access medicines.
- The UK continues to be at the forefront of PV methodology. We strongly influenced the new legislation, have advanced signal detection software and are coordinating the new European Joint Action on PV project.
- UK has a strong tradition of voluntary health professional reporting and introduced patient reporting ahead of other European Member States. This culture of continuous feedback and learning in the NHS helps make the UK an attractive place to launch a medicine. The strength of UK PV and structure of the NHS meant the UK could provide a “controlled space” for patients on new drugs to be monitored.
- The group supports the use of epidemiological studies using data sources like CPRD to ensure the monitoring of the risk/benefit balance of medicines, especially introduced under adaptive licensing, protects patients and public health.

### **3.8. Supporting the wider innovation agenda**

#### **3.8.1. Red Tape Challenge**

3.8.1.1. MHRA participated in the Red Tape Challenge in March – April 2012 and the theme was publically reported in March 2013 to launch a programme of mainly non-legislative simplification in the lifetime of this parliament.<sup>12</sup> Industry largely validated the European legal framework for medicines, and comments focussed on process changes to licences and non-statutory guidance, which are being addressed in a programme of work agreed with Cabinet Office.

### 3.8.2. Innovation Office

3.8.2.1. The MHRA's Innovation Office<sup>13</sup> was established in March 2013 as part of the UK Government's industrial strategy for life sciences which is designed to help overcome barriers and create incentives for the promotion of healthcare innovation. The Innovation Office is in addition to the existing services the MHRA offers to support innovation, namely various helplines, scientific advice, workshops, guidance etc.

3.8.2.2. It was recognised that innovative products or technologies are often developed by academics or SMEs who have little or no regulatory affairs expertise. The type of products or approaches that would be covered by the Innovation Office include regenerative medicine or Advanced Therapy products, nanomedicines, novel drug device combinations, novel manufacturing methods, etc, and it is indeed these areas that existing queries have covered.

3.8.2.3. To date, the queries have come from a wide range of organisations; the largest category was SMEs (approx 33%), followed by consultants, academics and pharmaceutical companies. The most popular topic has been medical

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<sup>12</sup> <http://www.mhra.gov.uk/NewsCentre/CON254836>

<sup>13</sup> <http://www.mhra.gov.uk/Howweregulate/Innovation/index.htm>

devices (approx 50%) and in particular the use of software in devices, but there have also been questions on the use of stem cells in an Advanced Therapy product for heart disease, novel oral vaccine delivery methods, innovative manufacturing technologies and novel drug formulations.

3.8.2.4. The Office was receiving around one query a week. It was difficult to know what an optimum number was. Members were not unduly worried by the current levels of interest, and expected to see greater demand as awareness increased. MHRA planned to do some publicity to coincide with publication of the group's report.

### **3.8.3. Joint NICE/MHRA advice meetings**

3.8.3.1. The MHRA and NICE had set up a pilot system in March 2010 for joint advice meetings with companies. This would result in parallel advice from MHRA on medicines licensing issues and NICE on HTA issues. It would facilitate discussions at an earlier stage on HTA aspects and there are similar initiatives in other European Member States.

3.8.3.2. MHRA said there had only been one joint NICE/MHRA advice meeting. MHRA and NICE proposed to relaunch and rejuvenate this scheme at the time of the Expert Group report in September. There could be a broader discussion of the types of data that will come with an initial decision, new criteria and CPRD invited to meetings. The Scottish Medicines Consortium (SMC) and The All Wales Medicines Strategy Group (AWMSG) could be invited as well. These suggestions were welcomed by the group.

### **3.8.4. Communications plan to support wider innovation**

3.8.4.1. As highlighted in this report, the group concluded that changes to the legal framework for evaluation of medicines

for quality, safety and efficacy are not currently required. Rather there is a need to ensure that certain organisations developing innovative medicines understand the regulatory and wider landscape and that regulators continue to engage with stakeholders to ensure the regulatory framework remains current. For this reason the Expert Group has recommended to the MHRA that a communications plan be developed to address this.

3.8.4.2. Key messages for MHRA to consider in communicating this work were:

- The drivers behind the need for innovation in regulation
- The MHRA's current work to support innovation.
- Together with the National Institute for Health Research and its Office for Clinical Research Infrastructure (NOCRI), promotion of the excellent facilities the UK has to support the development of new products ( e.g. via its experimental medicine research infrastructure and clinical research networks).
- The CPRD as a source for public health data (with an appropriate level of governance to protect patient privacy), a tool for pharmacovigilance, clinical trials feasibility and planning, and a signpost or portal to other sources of health-related and biomedical data of value to medicines development.
- The experience, knowledge and skills resources of The National Institute for Biological Standards and Control (NIBSC) in the field of biological medicines, which has been part of MHRA since April 2013.
- The existing flexibilities within the licensing regime, and MHRA's willingness to discuss and advise applicants on such flexibilities.

- How the EU system compares with the US system to support innovative products and similar tools available.

## **4. Background information on the *Expert Group on innovation in the regulation of healthcare***

### **Role and Terms of Reference**

4.1. Terms of reference of the group agreed by the health minister The Rt Hon Earl Howe are at Annex i.

### **Meetings and operation**

4.2. Meetings were held on the following dates:

27<sup>th</sup> June 2012  
9<sup>th</sup> October 2012  
29<sup>th</sup> January 2013  
16<sup>th</sup> April 2013  
16<sup>th</sup> July 2013  
25<sup>th</sup> September 2013

4.3. Meetings were held at the MHRA offices at 151 Buckingham Palace Road, London SW1Q 9SZ. Members were not paid an attendance or preparation fee. Reasonable travel expenses were paid in accordance with standard MHRA policy.

4.4. The DH Minister for medicines policy, The Rt Hon Earl Howe, attended the second meeting of the group in October 2012.

### **Membership and Member Biographies**

4.5. Membership was agreed by ministers and letters of appointment sent from the Expert Group chairman. A list of members is at Annex vi.

## **Annex i: Terms of Reference**

The Strategy for UK Life Sciences committed to pulling together a group of experts from government, regulators, the NHS, industry, and the academic and third sector communities to discuss healthcare regulation, including the development of new initiatives and innovations. The Strategy recognised that work to lead the debate on regulatory innovation would be ongoing, with the Ministerial (Biopharmaceutical) Industry Strategy Group Innovative Technology Forum providing an annual report to DH and BIS ministers. The report will set out measures of performance such as the use of conditional authorisation pathways, and uptake of the Early Access Scheme, alongside 'next steps' proposals for further regulatory innovation. The expert group will provide advice and guidance to the wider forum on issues relating to innovation and initiatives in safety, quality and efficacy regulation, including providing recommendations on how performance could be meaningfully measured and how the Agency could improve responses to regulatory innovations in future.

These terms of reference, including the purpose and scope of the group, will be discussed at an initial scoping workshop. The workshop will be followed by regular quarterly meetings as set out in the Life Sciences Strategy, and subject to the agreement of the members, publish a set of reports with recommendations to coincide with the 4<sup>th</sup> regular meeting (September 2013).

### **Purpose**

The initial focus of the group, and the first two sessions in particular, will be on two practical issues, and a wider exploration and definition of the issues in this area:

- Maximising the impact of, and learning from, the Early Access Scheme consultation;

- Developing the understanding of existing routes for early product availability, building on the existing work to meet the Life Sciences Strategy commitment
- Exploring and defining the wider regulatory problems which innovation and new initiatives are seeking to resolve.

There are a number of interrelated and connected areas which the group may wish to consider in relation to the exploration of wider regulatory problems, including those set out below. Exploring deficiencies in these areas and the potential wider impact will help develop an understanding of the system wide influences on drug development and how these interact with the regulatory process.

- The clinical trial environment in the UK;
- Defining unmet need, and the relation to regulation;
- Determinants of productivity challenges in drug development;
- Improving drug development decision making processes;
- Interaction with development incentives, such as orphan medicines or supplementary protection certificates;

### **Role and function**

Given the potential range and depth of issues under consideration, and the need to build focus and momentum, the group will operate as a task and finish group, delivering recommendations on the potential next steps for regulation within a defined timetable.

The remit of the group will be to explore potential actions and activity which the MHRA as safety, quality and efficacy regulator could undertake in relation to the above areas. This will include making practical recommendations for the implementation within existing legislation, or highlighting areas for potential further exploration at an EU level. In developing proposals the expert group will need to be aware of the wider determinants of drug development and approval, and may wish to highlight interdependencies and

areas where progress is, or could be, restricted due to issues outside the remit of the regulator. A number of limitations on existing policies in the areas for consideration are beyond the remit of the regulator and these could helpfully be highlighted as issues for further exploration through other channels. However, maximising the potential impact of the group will benefit from the discipline of maintaining a focus on areas of potential improvement within the remit of the Agency.

### **Timetable and deliverables**

A key task of the group will be exploring the potential 'next steps' for regulation, and how the regulator might wish to respond to new initiatives or innovations. Ensuring that there are tangible and practical recommendations produced will be key to meeting this objective. One year after the initial quarterly meeting (September 2013) the expectation is that the group will agree a set of concise reports on each of the areas under consideration, describing the evidence and learning from progress and experience to date in those areas, and make recommendations on how the approach to regulation could be further improved in future. The inclusion of relevant international comparisons within the report will be a key factor in ensuring the recommendations can help contribute to the growth agenda. The expectation is that initial drafts will be available for discussion at the 3<sup>rd</sup> quarterly meeting (June 2013).

## **Annex ii: Paper considered by the Expert group in April 2013 on *Regulatory tools and incentives designed to encourage and promote innovation***

### **United Kingdom**

Regulatory tools specifically in the UK designed to encourage and promote innovation include the recently formed innovation office.

#### *UK Innovation Office*

Building on previous experience, the Medicines and Healthcare products Regulatory Agency (MHRA) has recently launched an Innovation Office to help organisations navigate the regulatory processes in order to progress their products or technologies (innovative medicines, medical devices or novel manufacturing processes). The aim of the office is to promote early dialogue with innovative organisations and facilitate the understanding of the regulatory framework applicable to their innovation. For more information see: <http://www.mhra.gov.uk/Howweregulate/Innovation/index.htm>

#### *Scientific advice and guidance documents*

The MHRA offers a scientific advice service that can be requested at any stage of the development of a medicinal product, providing input and expertise into the challenges in progressing candidate molecules, in face to face meetings (257 meetings in 2011). Meetings can focus on quality, safety and/ or clinical development, development of paediatric forms, drug device combinations, pharmacovigilance advice and reclassification meetings. A broader scope meeting is also available, where general approaches to development plans can be discussed, and the MHRA and NICE have initiated a voluntary parallel scientific advice pilot. In terms of accessibility, the MHRA's Clinical Trials Unit has a dedicated helpline to assist sponsors with their applications and the Regulatory Information Service (RIS) for medicines acts as the single main point of contact for the marketing authorisation holders of medicines. The MHRA also contributes expertise to symposium and conferences, for example the Joint BIA/MHRA Conference on Innovation in the development and regulation of biopharmaceuticals, June 2013. The MHRA produces a wide range of publications to provide guidance to the industry on the regulation of devices and medicines.

#### *Expertise within the Agency - scientific and regulatory*

The MHRA is one of the largest competent authorities in Europe, with scientific staff in non-clinical, quality, statistical, pharmacokinetic and medical areas. Many of the scientific staff are recognised internationally for their expertise and represent the MHRA on numerous external committees and at conferences and scientific meetings. The UK also benefits from a number of internal advisory committees, including the Commission on Human Medicines (CHM), chaired by Prof Stuart Ralston. Part of the CHM's role is to advise the MHRA in relation to the quality, safety and efficacy of human medicinal products. The Commission is supported in its work by Expert Advisory Groups (EAGs) covering various therapeutic areas (for example Biologicals, Oncology and Haematology, Paediatric medicines).

### **European**

Regulatory tools that are pan-European include the Innovation Task Force, provision of scientific advice, licensing flexibilities such as conditional approval, incentives for special populations (orphan and paediatric drugs) and a small and medium sized enterprises office.

#### *Innovation Task Force (ITF) at the European Medicines Agency (EMA)*

The ITF is a multidisciplinary group set up at the European Medicines Agency (EMA) to establish a discussion platform for early dialogue with applicants, to proactively identify scientific, legal and regulatory issues of emerging therapies and technologies. The group aims to address the impact of emerging therapies and technologies, identify the need for specialised expertise at an early stage and to provide regulatory advice to applicants.

#### *Scientific advice and guidance documents*

The EMA's Committee for Medicinal Products for Human Use (CHMP) prepares scientific guidelines in consultation with regulatory authorities in the EU Member States, to help applicants prepare marketing-authorisation applications for human medicines. These guidelines provide a basis for practical harmonisation of how the EU Member States and the Agency interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy.

The UK actively contributes to European scientific advice via CHMP's Scientific Advice Working Party (SAWP). The UK was co-ordinator for 129 procedures for the financial year 2011-12 (the lead member state in Europe).

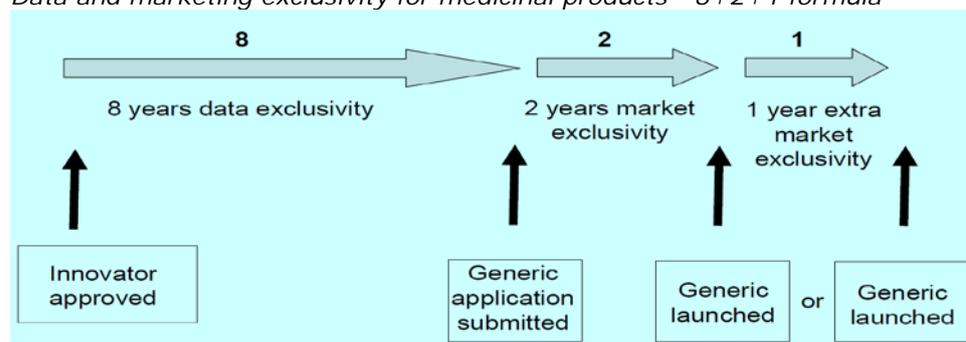
#### *Licensing routes for medicinal products*

According to European legislation, medicinal products for human use may only be placed on the market in the EU if a marketing authorisation has been issued by the Community (via CHMP and the European Commission) or by a competent authority of a Member State (MS) (for example, the MHRA). The vast majority of innovative products go through the centralised procedure, which results in a single marketing authorisation valid across all Member States of the EU. In order to meet unmet medical needs of patients, it may be possible to grant a marketing authorisation on the basis of less complete data than is normally required; a conditional approval. In addition, a licence under exceptional circumstances may be approved if the Applicant can demonstrate that he is unable to provide comprehensive data on the safety and efficacy under normal conditions of use (e.g. orphan drugs). An accelerated assessment procedure is also available for medicinal products that are expected to be of major public health interest, particularly from the point of view of therapeutic innovation (see Annexed paper for further information).

#### *Data and marketing exclusivity for medicinal products (Directive 2001/83/EC)*

Market protection for originator pharmaceuticals results in periods of exclusivity, both data and market. For data exclusivity, an applicant of a generic product cannot refer to the results of pre-clinical tests and clinical trials of the innovator medicinal product if it has been authorised for less than eight years. Furthermore, a generic medicinal product cannot be placed on the market until ten years have elapsed from the initial authorisation of the innovator product (market exclusivity). The ten-year period can be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which are deemed to provide a significant clinical benefit in comparison with existing therapies.

#### *Data and marketing exclusivity for medicinal products - 8+2+1 formula*



#### *Paediatric Regulation (Regulation 1901/2006)*

The paediatric regulation established a system of obligations, rewards and incentives for products developed in the paediatric population. The incentives include the provision of free scientific advice provided by the European Medicines Agency (EMA) as an incentive to sponsors developing medicinal products for the paediatric population.

Where a marketing authorisation application includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the holder of the patent or supplementary protection certificate is entitled to a six-month extension. There is also provision for a one-year extension of the period of marketing protection for a medicinal product, on the grounds that a new paediatric indication brings a significant clinical benefit in comparison with existing therapies.

In order to establish incentives for authorised products no longer covered by intellectual property rights, a new type of marketing authorisation, the Paediatric Use Marketing

Authorisation was established (PUMA). A PUMA is granted through existing marketing authorisation procedures but must apply specifically for medicinal products developed exclusively for use in the paediatric population. PUMAs are associated with 10 years of market exclusivity and relate to medicines that are:

- already authorised;
- no longer covered by intellectual property rights (patents or supplementary protection certificates);
- to be exclusively developed for use in children.

#### *Orphan medicinal products (Regulation 141/2000)*

The orphan regulation provides incentives for the research, development and placing on the market of designated orphan medicinal products. A special contribution from the Community is allocated every year to the EMA and the contribution is used exclusively by the EMA to waive, in part or in total, regulatory fees payable.

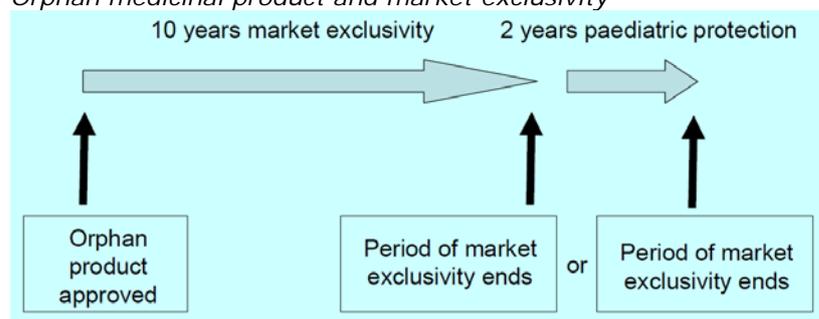
The sponsor of an orphan medicinal product may request scientific advice from the EMA on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product (so called protocol assistance).

In terms of protection of the innovation, Member States shall not for a period of 10 years grant a marketing authorisation for the same therapeutic indication, in respect of a similar medicinal product (10 years of market exclusivity).

#### *Paediatric and orphan medicinal products*

Medicinal products designated as orphan gain ten years of market exclusivity on the granting of a marketing authorisation for the orphan indication. The ten-year period of orphan market exclusivity is extended to twelve years if the requirement for data on use in the paediatric population is fully met.

#### *Orphan medicinal product and market exclusivity*



#### *Advanced Therapies (Regulation 1394/2007)*

Science evolves very rapidly in the advanced therapies field. As an incentive, the fee for scientific advice should be kept at a minimal level for small and medium-sized enterprises, and should also be reduced for other applicants. A 90% reduction for small and medium-sized enterprises and 65 % for other applicants shall apply to the fee for scientific advice payable to the EMA for any advice given in respect of advanced therapy medicinal products.

Studies necessary to demonstrate the quality and nonclinical safety of advanced therapy medicinal products are often carried out by small and medium-sized enterprises. As an incentive to conduct those studies, a system of evaluation and certification of the resulting data by the EMA, independently of any marketing authorisation application, has been introduced. Even though the certification is not legally binding, this system is aimed at facilitating the evaluation of any future application for clinical trials and marketing authorisation application based on the same data.

#### *Micro, small and medium-sized enterprises (Regulation 2049/2005)*

Small and medium-sized enterprises (SMEs) operating in the pharmaceutical sector are often innovative companies and the EMA's SME office has the remit of offering assistance to SMEs. Incentives offered to SMEs include:

- Administrative and procedural assistance from the SME Office
- Fee reductions for scientific advice, scientific services and inspections
- Fee exemptions for certain administrative services of the Agency
- Deferral of the fee payable for an application for marketing authorisation or related inspection
- Conditional fee exemption where scientific advice is followed and a marketing authorisation application is not successful
- Assistance with translations of the product information documents submitted in the application for marketing authorisation

### **Annex: Licensing routes**

There are four routes to licensing medicinal products (marketing authorisation), national, Decentralised procedure, Mutual Recognition procedure and the Centralised procedure. Legislation requires that marketing authorisation for a medicinal product shall be refused if:

- the risk-benefit balance is not considered to be favourable; or
- its therapeutic efficacy is insufficiently substantiated by the applicant; or
- its qualitative and quantitative composition is not as declared.

The benefit risk balance is defined as an evaluation of the positive therapeutic effects of the medicinal product in relation to any risk relating to the quality, safety or efficacy, as regards patients' health or public health. Licensing authorities, when concluding on the benefit risk profile, must find a balance between the need to ensure adequate data on a new medicinal product for a robust regulatory decision and the requirement for rapid access to new therapies.

#### **National procedure**

Each EU Member State has its own procedures for the authorisation of medicines that fall outside the scope of the centralised procedure. In the UK, a company submits a marketing authorisation application to the MHRA (it is also possible to submit parallel national procedures in several member states at the same using either the MRP or DCP procedures - see below). The application is reviewed by a team of assessors with an outcome of grant, grant with conditions, grant under exceptional circumstances or refuse. A fast track assessment procedure is available for products that are considered to provide a major breakthrough in the treatment of patients for certain conditions.

<http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Informationforlicenceapplicants/Fasttrackingofmarketingauthorisationapplications/index.htm>

#### **Mutual recognition procedure**

A medicine is first authorised in one EU Member State, in accordance with the national procedures of that country. Following this, further marketing authorisations can be sought from other EU countries in a procedure whereby the countries concerned agree to recognise the validity of the original, national marketing authorisation.

#### **Decentralised procedure**

Companies may apply for simultaneous authorisation in more than one EU country for products that have not yet been authorised in any EU country and that do not fall within the mandatory scope of the centralised procedure.

#### **Centralised procedure**

The European Medicines Agency is responsible for the 'community authorisation procedure' or centralised procedure (mandatory for certain types of medicines). The application is assessed by the Committee for Medicinal Products for Human Use (CHMP), where the UK is fully represented. A single marketing authorisation is valid across all Member States of the

EU if approval is granted at the end of a Centralised Procedure. The rationale behind the centralised procedure is that important medicines are automatically licensed in every EU Member State rather than a limited number of countries. It is compulsory for new drugs in the following areas to be licensed via the Centralised Procedure:

- Biotechnology
- HIV/Aids
- Oncology
- Diabetes
- Neurodegenerative disorders
- Autoimmune diseases and other immune dysfunctions
- Viral diseases
- Officially designated 'orphan medicines'

It is optional in other circumstances

- Other new active substances
- 'Others' deemed of significant therapeutic, scientific or technical innovation, or if the authorisation would be in the interest of public health at community level – "community interest"

The centralised procedure results in a Commission decision, which is binding on all EU Member States. In reality, the vast majority of innovative products go through the centralised procedure for assessment/authorisation.

#### ***Accelerated assessment***

An Applicant can apply for an accelerated assessment procedure, for medicinal products that are expected to be of major public health interest, particularly from the point of view of therapeutic innovation.

#### ***Conditional marketing authorisation***

For certain categories of medicinal products going through the centralised procedure, in order to meet unmet medical needs of patients and in the interest of public health, it may be necessary to grant marketing authorisations on the basis of less complete data than is normally required. In such cases, it is possible for the CHMP to recommend the granting of a marketing authorisation subject to certain specific obligations to be reviewed annually ('conditional marketing authorisation').

- Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;
- Medicinal products to be used in emergency situations, in response to public threats
- Medicinal products designated as orphan medicinal products

The granting of a conditional marketing authorisation will allow medicines to reach patients with unmet medical needs earlier than might otherwise be the case, and will ensure that additional data on a product are generated, submitted, assessed and acted upon. It is expected that the applicant will complete the development process and in due course the conditional approval will be converted into a normal approval. Some recent examples of Conditional MA include:

- Caprelsa (vandetanib, 2012) approved for the treatment of medullary thyroid cancer. The pivotal study was a phase II-III, randomised, double-blind, placebo-controlled trial in 331 patients. As a condition of the MA, the marketing authorisation holder (MAH) was required to submit the results from an open label CHMP approved protocol study, comparing RET negative and RET positive patients
- Pixuvri (pixantrone, 2012) approved for the treatment of Non Hodgkin cell Lymphomas (NHL). The pivotal study was an open-label, randomised, comparative trial in 140 patients. As a condition of the MA, the MAH was required to conduct a randomised controlled Phase III study of pixantrone-rituximab vs gemcitabine-rituximab in patients with aggressive B-cell NHL
- Fampyra (fampridine, 2011) approved for treatment of multiple sclerosis. The pivotal studies were double-blind, placebo-controlled and included 540 patients. As

a condition of the MA, the MAH was required to conduct a double-blinded, placebo-controlled, long-term efficacy and safety study to investigate a broader primary endpoint, clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide treatment

- Arzerra (ofatumumab, 2010) approved for the treatment of chronic lymphocytic leukaemia (CLL). The pivotal study was an open-label, single arm study in 154 patients. As a condition of the MA, the MAH was required to submit an open label, multicentre study investigating the safety and efficacy of ofatumumab therapy versus physicians' choice in patients with bulky fludarabine refractory chronic lymphocytic leukaemia (CLL) and to submit a phase IV observational study to provide further data on the clinical efficacy and safety of ofatumumab

The Table below lists the currently active conditional approvals in the EU.

Medicine	Authorisation date
Pixuvri	10/05/2012
Caprelsa	17/02/2012
Votubia	02/09/2011
Fampyra	20/07/2011
Votrient	14/06/2010
Humenza	08/06/2010
Arzerra	19/04/2010
Arepanrix	23/03/2010
Intelligence	28/08/2008
Tyverb	10/06/2008
Vectibix	03/12/2007
Diacomit	04/01/2007

The standards for Conditional MA are not identical to related schemes in other regulatory regions, in particular for 'accelerated approval' in the US for which approval can be based on surrogate endpoints 'reasonably likely to predict clinical benefit'.

#### ***MA under Exceptional circumstances***

For licensing under exceptional circumstances, the Applicant must demonstrate that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use:

- The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- In the present state of scientific knowledge, comprehensive information cannot be provided, or
- It would be contrary to generally accepted principles of medical ethics to collect such information,

Under these circumstances an authorisation may be granted with a reduced clinical data package than would ordinarily be required. Some recent examples of MA granted under exceptional circumstances include:

- Vyndaqel (tafamidis meglumine, 2011) approved for treatment of familial amyloid polyneuropathy. The pivotal study was a phase II/III, randomised, double-blind, placebo-controlled trial in 128 patients
- Ilaris (cankinumab, 2009) approved for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS). The pivotal study was an open-label run-in phase trial in 35 patients
- Elaprase (idursulfase, 2007) Approved for the treatment of Hunters Syndrome. The pivotal study was a double-blind, randomised, placebo/dummy-controlled in 96 patients

The Table below lists the currently active exceptional circumstances approvals in the EU.

Medicine Name	Authorisation date
Vyndaqel	16/11/2011
Firdapse (previously Zenas)	23/12/2009
Ilaris	23/10/2009
Rilonacept Regeneron	23/10/2009
Foclivia	19/10/2009
Pandemic influenza vaccine (H5N1)	19/10/2009
Pandemic Influenza Vaccine (H5N1)	16/10/2009
Vedrop	24/07/2009
Ceplene	07/10/2008
Yondelis	17/09/2007
Atriance	22/08/2007
Increlex	03/08/2007
Daronrix	21/03/2007
Elaprase	08/01/2007
ATryn	28/07/2006
Evoltra	29/05/2006
Naglazyme	24/01/2006
Prialt	21/02/2005
Xagrid	16/11/2004
Onsenal	17/10/2003
Ventavis	16/09/2003
Aldurazyme	10/06/2003
Zavesca	20/11/2002
Xigris	22/08/2002
Replagal	03/08/2001

## Annex iii: Comparison of EU and USA licensing flexibilities

EMA	FDA
<p><b>Conditional approval</b></p> <ul style="list-style-type: none"> <li>Allows approval of a drug for serious or life threatening conditions based on less complete data than is normally required, subject to certain specific obligations to be reviewed annually</li> </ul>	<p><b>Accelerated approval</b></p> <ul style="list-style-type: none"> <li>Allows approval of a drug for serious or life threatening conditions based on an effect observed on a surrogate endpoint that is reasonably likely to predict clinical benefit</li> </ul>
<p><b>Approval under exceptional circumstances</b></p> <ul style="list-style-type: none"> <li>Applicants must demonstrate that they are unable to provide comprehensive data on the efficacy and safety under normal conditions of use (e.g. rare conditions)</li> </ul>	<p>No direct equivalent procedure</p>
<p><b>Accelerated assessment</b></p> <ul style="list-style-type: none"> <li>CHMP opinion given within 150 days as opposed to 210 days</li> </ul>	<p><b>Priority review</b></p> <ul style="list-style-type: none"> <li>Regulatory review period shortened from standard 10 months to 6 months</li> </ul>
<p><b>Similar supportive mechanisms to Fast track designation</b></p> <ul style="list-style-type: none"> <li>Innovation task force/ SME office/ CHMP scientific advice &amp; protocol assistance/ Qualification of novel methodologies for medicine development</li> </ul>	<p><b>Fast track designation</b></p> <ul style="list-style-type: none"> <li>Facilitate development and expedite review of drugs through more frequent FDA interaction and rolling review of data</li> </ul>
<p><b>Similar supportive mechanisms to breakthrough designation</b></p> <ul style="list-style-type: none"> <li>Innovation task force/ SME office/ CHMP scientific advice &amp; protocol assistance/ Qualification of novel methodologies for medicine development</li> </ul>	<p><b>Breakthrough designation</b></p> <ul style="list-style-type: none"> <li>Expedite the development and review of drugs through more intensive FDA guidance and commitment to involve senior management</li> </ul>
<p><b>Orphan Designation</b></p> <ul style="list-style-type: none"> <li>A supportive legislative framework for medicines for rare diseases was adopted in Europe in 2000 (Regulation (EC) 141/2000). Although similarities exist, the criteria and processes for designation are not internationally harmonised. However, a common joint EMA/FDA orphan designation application form is available</li> </ul>	<p><b>Orphan Designation</b></p> <ul style="list-style-type: none"> <li>A supportive legislative framework for medicines for rare diseases was adopted in the USA in 1983 (the Orphan Drug Act).</li> </ul>

## Annex iv: Comparison of Breakthrough therapy designation and MHRA processes

Breakthrough therapy designation characteristic	Equivalent MHRA activity
Holding meetings with the sponsor and the review team throughout the development of the drug.	The MHRA offers a scientific advice service in face to face meetings, which can be requested during any stage of the development of a medicinal product.
Providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable.	<p>Following a scientific advice meeting, a final scientific advice letter is sent to the company within 30 working days of the meeting.</p> <p>The MHRA has launched an 'Innovation Office', aimed at providing regulatory advice and to support research and development.</p> <p>The EU system also provides extensive guidance to applicants outlining requirements</p>
Taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment.	<p>National scientific advice covers aspects such as endpoints, trial duration, target population, choice of comparator and statistical methodology.</p> <p>EMA scientific advice provides similar advice</p> <p>The MHRA's dedicated clinical trial unit carries out timely approval of clinical trial applications, 100% within statutory timelines.</p> <p>The MHRA has strong expert representation on European committees including Committee on Human Medicinal Products (CHMP) and Scientific Advice Working Party (SAWP).</p>
Assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the cross-discipline members of the review team (i.e., clinical, pharmacology-toxicology, chemistry, manufacturing and control (CMC), compliance) for coordinated internal interactions and communications with the sponsor through the review division's Regulatory Health Project Manager.	Internal MHRA procedures are in place to ensure quality and consistency of the final scientific advice letters (multi-disciplinary in house review group). MHRA has dedicated product life cycle assessment teams (PLATs) for different therapeutic areas, comprising clinical, non-clinical and pharmaceutical assessors and the same specialist assessors handle products throughout the licensing process. The MHRA clinical trials unit works alongside the PLATs and are also present at scientific advice meetings, along with statistical and standards/inspection colleagues as required.

<p>Involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review</p>	<p>National scientific advice meetings are carried out by experienced staff and procedures have management oversight. European scientific advice is similarly prepared by experienced assessors and adopted through CHMP.</p>
<p>FDA publishes the <u>number</u> of requests made, granted or denied since the enactment of FDASIA on July 9, 2012, but not the specific products or the 'indication' for which the investigational medicine received the breakthrough designation. Under FDA regulations, it cannot disclose information submitted to an investigational new drug (IND) filing.</p>	<p>Names of specific products undergoing advice are not released, however numbers of advice procedures are released.</p>

## **Annex v: Summary of the UK proposal for an Early Access to Medicines Scheme**

1. The 2011 Prime Minister's Life Sciences strategy included a commitment for Government to consult on an early access scheme.<sup>14</sup> The consultation ran from 13 July to 5 October 2012 and included an impact assessment and draft guidance for applicants.<sup>15</sup> The consultation responses have been assessed and considered by the Expert Group. MHRA has developed a procedure for review of Early Access applications so that it is in a position to launch the scheme when agreed. The outcome to consultation will be published when agreed across Government.
2. Early Access is a national scheme to support supply of highly promising unlicensed medicinal products in areas of high unmet medical need within the UK at a stage in their development where they are nonetheless deemed to be sufficiently safe and efficacious. As such, it is clearly distinguished from ideas being developed under the "Adaptive Licensing" pilot project, since Adaptive Licensing relates, at least in terms of the regulation of quality, safety and efficacy, to the pro-active use of existing flexibilities in the EU licensing rules.
3. Under the scheme the Medicines and Healthcare products Regulatory Agency (MHRA) would issue an opinion on the risk:benefit profile of the product to inform prescribing by clinicians. Responsibility would remain with the prescriber as is the normal case with unlicensed medicines.

### **Key features of the Early Access proposal**

- It will operate within the current regulatory structure and is voluntary and non-statutory;
- MHRA will provide a scientific opinion on promising new medicines that will treat, diagnose or prevent life threatening, chronic or seriously debilitating conditions without adequate treatment options before they are licensed;
- It is conditional on data from the development process of the product that indicates that the benefit:risk profile of the medicine is positive. The scheme will be limited to medicines representing a significant advance in treatment in an area of unmet need;
- The scientific opinion will describe the benefits and risks of the medicine, based on information submitted to the MHRA by the applicant;
- The opinion will be made available on the MHRA's website to assist clinicians and patients in making treatment decisions, and to support informed consent by patients to the risks and benefits of the product as far as these have been identified in the development process for the product.

<sup>14</sup> <http://www.bis.gov.uk/assets/biscore/innovation/docs/s/11-1429-strategy-for-uk-life-sciences>

<sup>15</sup> <http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MLXs/CON173755>

## **Annex vi: Membership of the Expert Group**

### **Prof. Sir Kent Woods (Chair)<sup>16</sup>**

Chief Executive Officer, Medicines & Healthcare products Regulatory Agency

### **Dr Ian Hudson (Chair)<sup>17</sup>**

Chief Executive Officer, Medicines & Healthcare products Regulatory Agency

### **Dr Christiane Abouzeid PhD**

Head of Regulatory Affairs, BioIndustry Association (BIA)

### **Mr Steve Bates**

CEO, BioIndustry Association

### **Sir John Bell<sup>18</sup>**

University of Oxford

### **Ms Jane Belfour**

Head of Sector Policy Office for Life Sciences , Dept for Business, Innovation and Skills

### **Ms Christine Bloor<sup>19</sup>**

Office for Life Sciences, Dept for Business, Innovation and Skills

### **Dr Kieran Breen<sup>20</sup>**

Director of Research & Innovation, Parkinson's, UK

### **Sir Ian Carruthers**

Chief Executive, NHS South of England

### **Mr Giles Denham**

Director Medicines, Pharmacy and Industry Group, Department of Health.

### **Dr Mark R Edwards BSc MB BS FRCA FSB**

R&D Director, Ethical Medicines Industry Group (EMIG)

### **Mr Ivan Ellul<sup>21</sup>**

NHS England

### **Professor Stephen Evans**

London School of Hygiene and Tropical Medicine

### **Dr Tom Foulkes, MA (Cantab) PhD**

Programme Manager: Experimental Medicine  
Medical Research Council, UK

### **Dr Sarah Garner PhD BPharm MRPharmS**

Centre for the Advancement of Sustainable Medical Innovation

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<sup>16</sup> Until retirement on 20 September 2013

<sup>17</sup> From 21 September 2013

<sup>18</sup> From January 2013

<sup>19</sup> Until January 2013

<sup>20</sup> From February 2013

<sup>21</sup> From April 2013

**Ms Penelope Green<sup>22</sup>**

Cabinet Office, Economic & Domestic Affairs Secretariat

**Dr David Griffiths-Johnson BSc, PhD, MBA**

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**Dr Esteban Herrero-Martinez BSc PhD**

Head of Regulatory Affairs, Association of the British Pharmaceutical Industry

**Dr Harpal S Kumar MA MEng MBA Dsc**

Chief Executive Officer, Cancer Research UK

**Professor Carole M Longson BSc PhD<sup>24</sup>**

Director, Centre for Health Technology Evaluation  
National Institute for Health and Care Excellence

**Mr Alan Morrison**

Chairman of BIA's Regulatory Affairs Advisory Committee and Vice-President, International Regulatory Affairs and Safety at Amgen

**Professor Norman Morrow<sup>25</sup>**

Chief Pharmaceutical Officer, Northern Ireland Government

**Dr Mark R Nelson MA MBBS FRCP**

Consultant Physician Chelsea and Westminster Hospital, London  
Honorary Senior Lecturer Imperial College London

**Dr Danny Palnoch (BSc Econ Hon)**

Senior Economic Adviser, Department of Health

**Professor Bill Scott**

Chief Pharmaceutical Officer, Scottish Government

**Dr Jayne Spink PhD**

Chief Executive, Tuberous Sclerosis Association

**Professor Roger Walker BPharm PhD FRPharmS FFPH**

Chief Pharmaceutical Officer for Wales

**Professor Ian V D Weller BSc MB BS MD FRCP Hon FRCP(Glasg)**

Emeritus Professor of Sexually Transmitted Diseases, Research Department of Infection and Population Health, University College London

**Dr K Louise Wood Bsc (Hons) PhD FFPM(Hon)**

Deputy Director, Head of Research Infrastructure and Growth, Research and Development Directorate, Department of Health

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<sup>22</sup> From April 2013

<sup>23</sup> Until April 2013

<sup>24</sup> From January 2013

<sup>25</sup> Until retirement in June 2013