

AGENDA ITEM 4**Emerging Science and Bioethics Advisory Committee****Focus Group on Regulations****Proposal to ESBAC****INTRODUCTION**

1. At the second ESBAC meeting, the Committee decided to set up four Focus Groups each to consider one of the four topics selected for possible work. These Groups met twice with the aim of scoping the feasibility of these areas of work.
2. Discussions from the Regulations Focus Group are reflected in this paper which proposes to ESBAC that *governance related issues in the context of the regulation of emerging technologies* should be included in ESBAC's work plan.
3. The reasoning behind this proposal is outlined below with reference to ESBAC's topic selection criteria, together with initial scoping information on the proposed approach including potential stakeholders, delivery mechanisms and deliverables. This is in line with Annex E of ESBAC's Code of Practice. The Membership of the Focus Group is included at Annex A.
4. ESBAC is invited to comment on this proposal and collectively agree whether the Committee is supportive of the proposal progressing.

PROPOSED APPROACH

5. Discussions at ESBAC meetings to date and at the Regulations Focus Group meeting have identified that developing regulatory responses to emerging biomedical science is challenging because public policy on biomedical innovation is shaped by multiple competing policy drivers¹.
6. Against the backdrop of a complex governance landscape, the Focus Group proposes the development of an overarching integrative governance framework to guide regulatory and policy decision making for emerging biomedical science and technology that takes account of the interactions between:

¹ Including for example, the need to improve public health by facilitating useful innovation; the need to protect public health by constraining harmful innovation; the desire to enhance national wealth and the need to constrain healthcare spending by limiting unnecessary expenditure on unproven healthcare technologies.

scientists/innovators; policy makers and government; and members of the public/stakeholder groups.

7. ESBAC could usefully develop guidelines for policy decisions on issues and examples that arise in this regulatory context, as the basis for a governance framework for innovative biotechnologies. These guidelines would also include ethical, social and economic considerations.

TOPIC SELECTION CRITERIA

8. The case for how this topic fulfils ESBAC's remit is summarised below:
 - ✓ **Relevant:** Emerging technologies and the governance approaches being applied to them can impact on innovation and translation, with the potential for ethical, legal, social and economic implications.
 - ✓ **Applicable to policy:** Many current governance-related initiatives² are designed to consider how to deliver smarter, faster, cheaper regulatory systems while continuing to ensure safety and efficacy. ESBAC could usefully contribute to policy decisions in these areas, as the basis for a governance framework for innovative biotechnologies. This also supports the health and wealth agenda.
 - ✓ **Timely:** No time constraints but this proposed contribution would certainly be timely in the light of ongoing developments in regulatory reform (eg. recast of the medical devices regulations). An initial broad framework could be developed where other issues and examples could be incorporated as they arise. For example, the House of Lords Science and Technology Committee Inquiry into regenerative medicine.
 - ✓ **Realistic:** The proposed work relies on the availability of ESBAC and sub-groups that may be set up and stakeholders to contribute.
 - ✓ **Unique:** Utilise Members' high-level strategic and inter-disciplinary expertise and readily apply this unique combination of knowledge to these issues of regulation, enabling ESBAC to develop a framework that could be applied to issues as they arise.

² Relevant issues here include: changes to the Clinical Trials Directive, MHRA/NICE interactions, medical devices and diagnostics regulation, early access to medicines and patient involvement in clinical trials, new developments in regulatory science

TOPIC FRAMING ISSUES**Scoping:**

9. A focussed and self-contained piece of work is proposed to develop a governance framework that could:
 - Scope the key issues surrounding innovation/governance/ethical interactions.
 - Help to enable cross-sector and cross-policy integration.
 - Identify opportunities to simplify and rationalise the governance landscape for health related innovations.
 - Pinpoint specific initiatives where this framework could be applicable.
10. In areas where there is significant activity by regulators or other statutory bodies, ESBAC would not duplicate work already underway, but may wish to comment on potential interactions across policy areas that could be relevant to overall guidelines.
11. Annex B, drafted by Focus Group members, outlines how the framework could be developed, and in particular suggests the types of questions to be addressed by the framework that could be translated into policy guidelines.

Stakeholders:

12. Although this is likely to be a piece of work led and developed by ESBAC Members themselves, it will be essential to involve the following key stakeholders:
 - MHRA
 - Health Technology Assessment
 - NICE
 - Health Research Authority

Deliverable(s) and Delivery Mechanism:

13. A governance framework to be placed in the public domain. The framework could contribute to delivery of safety, quality and efficacy of new biomedical technologies, in an ethical context, as well as stimulating innovation processes.
14. As part of the process ESBAC will also bring together stakeholders whether as a working group or as one off workshop. This could be a deliverable in itself.

Cross cutting themes

15. Overarching themes of particular relevance to this topic that would need to be given consideration if work was taken forward include the impact of regulation, consumer protection/safeguarding patients, governance and good practice, translation and societal impact.

QUESTIONS for ESBAC:

ESBAC is asked to comment on the proposal with a view to recommending whether or not this work should be taken forwards.

If ESBAC recommends that this work should be taken forwards, then it will wish to comment on the remit, scope and deliverables.

However, if ESBAC considers that this work should not be taken forward at this stage, the Committee will wish to record its reasons for its decision.

Annex A

Regulation Focus Group Members

Professor Joyce Tait (Champion)

Professor Sir Alasdair Breckenridge

Professor Bobbie Farsides

Dr David Townend

Ms Diana Sternfeld

Dr Dipti Amin

Professor Duncan McHale

Mr Julian Hitchcock

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Dr Stuart Hogarth

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Annex B

Proposal for development of a governance framework for emerging biomedical science and technology

1. Introduction

Discussions at Committee Meetings and Regulatory Focus Group Meetings have proposed a role for ESBAC to develop a framework to guide regulatory and policy decision making for emerging biomedical science and technology. ESBAC's remit, to "... *add value, interfacing science with ethical, social and economic implications to inform policy making*", suggests a role in contributing to development of health-related governance systems that, among other considerations, continue to meet societal health care needs while also enabling faster, more cost-effective development of new healthcare technologies.

The translation of innovation in health care technologies is currently governed by regulatory frameworks that have been established to ensure that products are safe and effective. However, there is increasing understanding of the ways in which regulation may also be used to encourage such translation without compromising safety. Relevant policy initiatives currently under way include:

- Development of a new clinical trials directive (planned Regulation, currently out for consultation);
- Recast of the medical devices regulations (including diagnostics);
- Development of EU regulations on pharmacovigilance;
- Addressing the 'red tape' challenge;
- Provision of early access to medicines (adaptive licensing);
- Adaptation of regulation relevant to stem cell research;
- Regenerative medicine, House of Lords Inquiry;
- Interactions between health technology assessment and regulation.

These and other initiatives are designed *individually* to contribute to a regulatory landscape that creates greater certainty, diminishes national vibrations, reduces gratuitous duplication and expedites procedures. However, there is an opportunity for ESBAC to develop an integrative framework that can guide policy makers facing the wide range of potential boundary-crossing interactions that can have such fundamental impacts (positive and negative) on the nature and timing of emergence of novel biomedical science and technology, and also on the broader scale and scope of national and international innovation systems.

2. Policy-Innovation Interactions

Policy on, and regulation of, biomedical innovation is shaped by multiple drivers: to improve public health by facilitating useful innovation; to protect public health by constraining harmful developments; to enhance national wealth by supporting industry; and to manage healthcare spending and limit

expenditure on unproven health technologies. The regulatory system can fail in two ways: it can be overcautious, unreasonably delaying approval of life saving medicines; or it can be insufficiently cautious, approving medicines that are ineffective or likely to cause harm. While the latter receives more publicity, the former can be equally serious.

In considering the interactions among these regulatory and policy drivers, different issues arise depending on the stage of development of the technology and the extent to which its impact is disruptive or incremental for the company developing it.

2.1 Disruptive technologies

A disruptive technology, seen from the perspective of the company developing it, is one that may lead to revolutionary improvements in healthcare or address unmet clinical needs, but will also challenge companies' established business models and innovation strategies. Regulation to ensure safety, quality and efficacy will be necessary but there may be no clear regulatory precedent. Alternatively, the presumed regulatory precedent may prove difficult to implement in the new context, for example stem cell therapies.

This tension between the incentives for companies to develop disruptive biomedical technologies and their capacity to do so is one of the main reasons for an increasing government focus on regulation and policy initiatives as the means to release the full innovative capacities of biotechnology-based industries.

Disruptive technologies also put pressure on policy makers and regulators to move their attentions upstream in the research and development process, sometimes to the extent of considering the nature of future regulatory systems in advance of a full understanding of the final properties of the technology. Such pressures arise from the perceived need to keep up to date with, or to anticipate, basic scientific discoveries, and from the needs of commercial investors for certainty about future regulatory systems before committing funding for a new technology.

2.2 Technology with incremental impacts

Most new healthcare technologies are products of incremental innovation and in these cases regulatory challenges arise from decades of accretion to regulatory systems as new, unexpected hazards have emerged. For example:

- In the late 1930s, the adulteration of an elixir of a sulphonamide with diethylene glycol (commercial antifreeze) as a substitute for more expensive glycerol resulted in the death of several hundred children in the US and occasioned the Food and Drug Act which specified that the contents of a medicine had to be appropriately labelled and of appropriate quality.

- The thalidomide disaster of the 1960s was the stimulus for a greater focus on safety and efficacy criteria for marketing authorisation of all new medicines, including particularly the need for teratogenicity testing.
- The UK experience in 2005 of the first administration of a novel monoclonal antibody TGN 1412 to six healthy volunteers, who suffered grave harm, was the stimulus for new regulations for first administration to man of perceived high risk compounds.

Such safety considerations have been complemented by an increasing need for efficacy data and more recently by the need for data generated during development also to meet the needs of health technology assessment bodies.

Current regulatory systems to ensure quality, safety and efficacy of medicinal products are lengthy and expensive and the cost of the resulting medicines has progressively increased so that the regulator has become, alongside the process of health technology assessment, one of the two key gatekeepers for access by patients and health care professionals to new medicines. These costs, and the inflexibility of regulatory systems, are limiting the number of potentially safe novel products that can be developed and is an important factor contributing to the difficulties companies experience in maintaining well-populated drug development pipelines. It is arguable whether such regulatory processes are an effective and efficient investment of scarce resources for the promotion of public health. Pressures for change from companies and patient groups are stimulating initiatives to consider how we could deliver smarter, faster, cheaper regulatory systems while continuing to ensure safety and efficacy.

One response to such pressures has been 'adaptive licensing' - granting marketing authorisation on the basis of less data than is currently required. Adaptive approaches proposed by regulatory authorities include 'progressive authorisation', 'managed entry', and 'staggered approval'. These are based on the evolving nature of knowledge about medicines, enabling replacement of the single transition from non-approval to approval by a series of stages with iterative phases of evidence gathering and phased regulatory approval. Adaptive approaches aim to facilitate early access to new technology, while acknowledging greater uncertainty about efficacy and safety. The acceptable levels of uncertainty to regulators will be predicated by considerations of the therapeutic area, medical need and stakeholder willingness to accept uncertainty. Evidence to reduce uncertainty comes from post marketing data, ensuring that the data are valid (e.g. patient adherence is high) and that the benefit-risk balance can be progressively assessed.

2.3 Biomedical science and technology in support of regulatory change

In addition to being the object of regulation, biomedical science and technology can have an important role in supporting regulatory change, to maintain safety and efficacy of products and processes while improving the efficiency of the regulatory systems themselves. Examples include: eliminating some aspects of a potential risk; providing faster, cheaper or more

ethical routes to generation of evidence for regulatory decisions; or adaptive licensing based on new scientific developments.

3 Stakeholder and Citizen Engagement/Dialogue

Public trust in regulatory systems has frequently been challenged by controversies over timely access to new medicines on one hand and on medicines withdrawals on the other, leading to demands for greater public involvement in regulatory decision making. More generally, engagement and dialogue with stakeholders and citizens are now routine components of technology assessment and governance. However, different engagement issues will arise depending on whether a new technology is incremental or disruptive.

For **disruptive technologies**, there is greater uncertainty about the eventual nature of products being developed and their costs and benefits, and they are more likely to challenge current societal norms, as well as pre-existing regulatory systems. It will be important to engage in dialogue with citizens who have no particular interest in the technologies themselves as well as with stakeholders such as patient groups who may be potential beneficiaries. **Incremental technology developments**, such as new drugs or diagnostic techniques, are less likely to raise fundamental societal issues but more likely to be of direct interest to patient groups.

The disruptive/incremental distinction that was applied above to future regulatory developments thus raises parallel issues in planning the nature and context for dialogue and engagement.

4 Development of a Governance Framework

An integrative governance framework relevant to ESBAC's remit could contribute to delivery of safety, quality and efficacy of new biomedical technologies as well as stimulating innovation processes, enabling a wider range of new technologies to reach a market place, and a wider range of innovative companies to prosper.

4.1 Questions to be addressed by the governance framework

The Framework would support policy makers faced with the following types of question.

Disruptive technologies

- How soon in the emergence of a new technology, is it appropriate to establish a regulatory pathway?
- Is there an appropriate regulatory precedent?
- What problems might emerge in its application?
- How can the proposed regulatory system be made adaptive to future unexpected scientific and technological developments?

- Should health technology assessment (HTA) be brought upstream so that it influences technology development much earlier in the process?
- Is it appropriate to allow users to influence the development of disruptive technologies at earlier stages in the process?

Technology with incremental impacts

- In which circumstances would accelerated approval of a drug be appropriate?
- What mechanisms could be used to maximise benefits and mitigate risks?
- Is it useful to create linkages between HTA and product licensing?

Biomedical science and technology

- Are there new technological developments that could help to minimise regulatory constraints?
- Would it apply to disruptive and/or incremental technologies?
- What new regulatory challenges might be raised by such products?
- How would such developments affect public and stakeholder perspectives on new technology?

Multi-level governance

- How can the UK government ensure that it has an effective voice in multi-level governance?
- What lessons can be learned from prior efforts at harmonisation early in the career of a new technology?
- How can citizens gain representation when regulatory policy is developed at the supra-national level?
- Are there general lessons to be drawn about the appropriate balance of powers between national and supra-national authorities?

4.2 Policy Guidelines

Development of the proposed governance framework will be a process of translating the above questions into policy guidelines. The framework to be developed will consist of guidelines to help policy makers respond to such questions, drawing on recent research on innovation/regulation/engagement interactions.

We suggest the following areas as test cases for the development of the general framework: **HTA interactions with regulatory systems; cell therapies; and pharmacogenomics/companion diagnostics.**