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SUMMARY REPORT OF THE OHE/EFPIA ANTIBACTERIAL ROUNDTABLE

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This is a summary of the main points and conclusions from a Roundtable organised by the Office of Health Economics for EFPIA, who funded both the events and the production of this Briefing. The views reproduced here are the author's synthesis of the discussions at the event (in which she participated) and have been agreed on that basis with the participants. Thus the arguments and views presented in the text, unless stated otherwise, cannot be attributed to any one of the Roundtable participants individually or to them all collectively. The author would like to thank James Anderson, Brendan Barnes, Jorge Mestre-Ferrandiz, Sophia Tickell and Adrian Towse for comments on earlier drafts.

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Introduction

Bacteria have developed resistance to almost every single antibacterial developed in the past 50 years or so and the rate of resistance to new antibacterials is increasing rapidly, with new "superbugs" emerging. Bacteria with the recently discovered New Delhi metallo-β-lactamase-1 (NDM-1) gene are resistant to the carbapenem class of antibacterials, some of the most powerful antibacterials currently available. The danger of resistant bacteria is that without effective treatment, diseases with traditionally high cure rates, such as pneumonia, become more difficult to treat. And "routine" procedures, such as organ transplants and hip replacement surgery, which rely on antibacterials, will carry a greater risk of failure.

Compounding the problem, in addition to the inappropriate use of antibacterials in both humans and animals, is the lack of new antibacterials in the pharmaceutical pipeline. Very few new classes of antibacterials have been discovered in the past decades. There are scientific and commercial reasons for this. The main commercial reason is the relatively low return on R&D investment in this area compounded by a necessarily restricted use of newer antibacterials, in order to manage resistance.

To encourage debate and understanding of the policy options, the Office of Health Economics (OHE) was asked by EFPIA[1] to organise two independent, but related events on the 6th of July 2011. In the morning, OHE launched its publication "New drugs to tackle antimicrobial resistance: Analysis of EU Policy Options", with keynote speakers commenting on the issues the report raised. In the afternoon, an expert roundtable[2] was convened to discuss a possible framework under which increased antibacterial R&D could be encouraged. It discussed issues in the OHE paper and other policy options that could be explored.

[1] European Federation of Pharmaceutical Industries and Associations.
[2] The Roundtable was moderated by Sophia Tickell from Meteos Ltd.

The objective was (i) to agree on the critical elements to be contained in any framework; (ii) to identify potential obstacles to their implementation; (iii) to consider how issues could be taken forward and, in particular, who is best placed to lead the exercise and who else needs to be involved.

Participants at both events included those from relevant services of the European Commission, EFPIA, individual biopharmaceutical companies, ReAct, Member State government departments and agencies, advocacy groups, and independent economists with considerable experience in the area. Annex 1 provides the full list of participants.

Morning Session: Presentation and Discussion of the OHE Report

Priya Sharma and Adrian Towse of OHE presented findings from their publication. The antibacterial resistance problem arises because of a fundamental market failure. Repayment of the resources used in antibacterial discovery requires appropriately large revenue, derived either from a high price or a large volume. On the one hand, a high price deters antibacterial use. On the other hand, a large market volume immediately brings about the possibility of the externality of greater development of resistance. In this case, the industry's traditional drug development model is flawed.

The Report evaluates the ways in which the market failure can be addressed. It analyses the economic impact of different push and pull incentives on the net present value of antibacterial R&D, to determine which incentives will be most effective at encouraging investment to generate novel antibacterials. The authors make two, non-mutually exclusive recommendations.

- First, they recommend a hybrid approach, similar to orphan drug legislation. The key incentives in this case are extended data exclusivity and a willingness of health care payers in Europe to allow higher prices for new antibacterials, to reflect the growing cost of antibacterial resistance. This should be accompanied by regulatory measures to accelerate approval and by restrictions on the use of new antibacterials to delay the build-up of resistance.

- Second, companies receive an upfront payment upon successful registration of a novel antibacterial via a mechanism such as an Advanced Market Commitment (AMC) or a transferable (wildcard) IP extension.

Chantal Morel from the London School of Economics (LSE) was invited to comment on the proposals. She welcomed both the attempt to quantify the problem and the fact that the paper was not assuming a business model that guaranteed blockbuster returns. She raised a number of technical concerns with the economic analysis, including a lack of detail around certain assumptions or parameters such as the discount rate, and the fact that a limited sensitivity analysis was conducted. In principle Chantal agreed with the OHE hybrid model; however, she did feel that it was important to move away from using the term "orphan-like" and towards something more antibacterial specific, such as "special designation for priority antibiotics", a title for a similar incentive she outlined in a paper for the ReAct seminar in May[3].

The ensuing discussion was wide-ranging and comprehensive and included the following discussion points:

What is a hybrid model?
There was general agreement with OHE's recommendation that a hybrid approach to solving the problem of antibacterial R&D was needed, ensuring that new initiatives respond in a targeted way to the specific bottlenecks in the research and development of new antibacterials. There were differences in stakeholder opinion about the meaning of the term, which would need to be clarified in future.

Market incentives in an EU context
There was a broad discussion about the desirability of addressing some of the core challenges identified in the OHE paper, including accelerated review at the EU and Member States level, improved health technology assessment (HTA), and pricing and reimbursement (P&R) reforms. However, much work is still needed to identify precisely how these would work, and participants expressed their concern about the feasibility of implementing change at the EU level, given that many of these processes are managed at the level of the Member State and there is limited EU coordination.

Advanced Market Commitments
Specific concerns were raised about the AMC. In particular, participants identified the fact that AMCs do not address the issue of incentives to market antibacterials outside the market to which the AMC is applied or once the AMC expires. They noted that the inclusion of a tail price, whereby the product is sold at cost once the AMC expired (a condition of some proposed AMC models), further strengthens the incentive to market the new antibacterial. The danger is that falling prices could lead to marketing to compensate for the decrease in price, thus expanding use

[3] A summary report of this seminar as well as presentations from the meeting are available for download from the ReAct website at: http://www.reactgroup.org/news/176/18.html

and increasing resistance. The OHE authors responded that the report addresses these concerns: it argues that any incentive should include measures to ensure and encourage appropriate use and stewardship and that an AMC can be designed to address the tail price and geographical issues.

Transferable IP extensions
Transferable IP extensions provide innovators with extensions of patent protection for commercially successful health technologies as compensation for undertaking R&D investments in priority disease areas characterised by poor profitability – in this case, antibacterials. They are a highly controversial mechanism and there was a lively discussion about the impact of using transferable IP extensions as an incentive. The OHE report argues that they would be a highly effective incentive, especially if applied to a blockbuster drug for a chronic disease. Concerns were raised about the ethical implications and political feasibility of shifting the cost to patients of the blockbuster drugs. This is of particular concern in markets were medicines are predominantly paid for out of pocket, which is not the case in Europe. Additionally, it was argued that transferable IP extensions have the unintended consequence of distorting the markets to which they are being applied by affecting competition between therapeutic substitutes and/or delaying generic entry.

Priority Review Voucher
An alternative possibility raised was that of a European priority review voucher (PRV) which would entitle any drug to which it is applied to an accelerated path to launch. This should include a rapid review from the European Medicines Agency (EMA) and guaranteed shorter timelines for P&R. For it to work, the PRV would require coordination between Member States, and they would need to ensure that the voucher guarantees the company a fast-track priority review through their P&R stages. One advantage of the EU PRV is that it extends the effective patent life of a drug by accelerating entrance to the market, but does not delay generic entry, as expiry dates remain unchanged.

From a commercial perspective, the EU PRV appears to be less attractive than a transferable IP extension and OHE's modelling suggests it would not incentivise antibacterial R&D on its own. However, as one participant noted, in so far as the EU PRV acts as a transferable IP extension complemented by accelerated review and shorter P&R timelines, it could, theoretically, be more attractive than OHE modelling suggested. This same participant did acknowledge that the transferable IP extension would be applied to a drug with known revenues while the EU PRV would be applied to a drug with no sales history, and that this difference in the level of uncertainty from the point of view of the PRV holder could lessen its comparative value.

Traditional business model versus a new R&D model
Towards the end of the morning session, participants began discussing the need for a new R&D model for antibacterials. It was generally agreed that the traditional business model was no longer working for antibacterials, especially as all the "low hanging fruit" (meaning blockbuster products discovered with standard R&D approaches) had been picked over many years. Several participants commented positively on the constructive approach of the pharmaceutical industry and their willingness to be flexible and creative in developing specific new approaches. It was noted that this was a historic shift and that the opportunity should not be lost. In particular, industry's suggestion that new models should separate the financial returns to companies from the volume of product used (thereby encouraging low volumes and appropriate use) was well received.

Afternoon Session: Building a Framework for Successful Antibacterial R&D

The afternoon discussions were focused on what it would take – politically and technically – to design and implement a new model for successful antibacterial R&D.

Political Considerations

Leadership and the Commission
EFPIA's motivation for sponsoring this roundtable event was multifaceted. Firstly, it believed that while much had already been done to move things forward, little had actually materialised. It attributed this to the fact that stakeholders did not want to confront the trade-offs that would need to be made in order to accomplish both conserving existing antibacterials and developing new ones. Secondly, EFPIA represents an industry that researches new treatments to meet public health needs and recognises the importance of developing new antibacterials. Thirdly, EFPIA wants to support the existing political momentum in the EU. And finally, because there is an economic and political dimension to this issue, EFPIA wanted to ascertain which incentives the different stakeholders thought were realistic and feasible, and also to understand what other stakeholders' concerns were so they can be incorporated into future discussions.

Throughout the whole day there was much discussion about how to translate all the debate into action, with a particular emphasis on who should take the lead. All

participants acknowledged the important leadership role that ReAct, with the support of the Swedish Government, has been taking in getting the issue onto the agenda and framing the debate. Now that this has been achieved, there was consensus that the Commission is best placed to assume leadership, as next steps will require coordination with multiple political and technical agencies as well as the involvement of individual Member States.

The Commission is already active on this issue. Through its Framework Programme, the Commission has already allocated more than €350 million over the past ten years for R&D against antibacterial resistance. In addition, new initiatives are currently being developed. Firstly, the Commission is working bilaterally with the US as part of TATFAR[4]. However, while TATFAR was lauded as a good first step towards coordinating solutions to antibacterial resistance, it was noted that cooperation between the US and the EU would need to extend beyond TATFAR, its members, and its remit.

Secondly, the Commission is working on its own five-year plan outlining how to address antimicrobial resistance. This plan will be released later this year. As part of this plan, the Commission has highlighted the issue of innovation and the need for effective antibacterials as one of the key points it wishes to tackle immediately.

Following the publication of its five-year plan, the Commission will begin to work on a more detailed action plan and it is here that they hope other stakeholders will become involved, playing critical roles in moving the agenda forward. The Commission has also launched a Joint Programming initiative in this area, which is attracting support from a significant number of Member States.

It was noted that the Commission has been successful in addressing similar problems in the past, for example, developing the European and Developing Countries Clinical Trial Partnership for Africa. One critical success factor there had been ensuring that all the right people were involved in the process.

Other Participants

Participants were asked to identify those stakeholders who, in addition to those who were already around the table, could help the Commission take appropriate action. Given that some of the discussion focused on regulatory reforms, the EMA was one of the first stakeholders identified.

Member State HTA and P&R agencies were the next group identified. Many of the incentives discussed during the roundtable will require their participation. Considering that, in the EU, HTA (and P&R) are dealt with at the Member State level, it will be important to seek and ensure the cooperation of each of the Member States' HTA and P&R agencies.

Similarly, any incentive(s) implemented will also require Member States' cooperation and buy-in. It was noted that Denmark will hold the EU Presidency in the second half of 2012, during which it plans to make antibacterial resistance a policy issue.

There was consensus that the pharmaceutical industry has a critical role to play going forward and that any initiative would need to harness its key capabilities and resources to develop novel antibacterials and bring them to the market. It was noted that this was most likely to be achieved if there were a successful balance between meeting payer and HTA needs as well as those of companies. It was noted that industry includes small and medium-sized enterprises (SMEs) as well as "large pharma", and they may have different needs along the value chain that should be addressed. Similarly, some incentives might be more valuable than others to SMEs. As a result, it will be important to ensure that their interests and concerns are noted as well.

In addition to the NGOs and academics attending the meeting, other groups identified were the veterinary sector and animal specific pharmaceutical companies, health care workers and prescribers, and patient and consumer groups.

Technical Considerations in the "New R&D Model" to Tackle the Lack of Antibacterials

Participants in the afternoon session highlighted a number of considerations that would need to be addressed when developing a 'new' R&D model to encourage antibacterial innovation. Such a new model would specifically need to provide solutions to the market failures and externalities identified in the OHE Report. The relevant considerations included scientific challenges; commercial considerations; the need for stewardship to prevent the development and spread of resistance; strong market signals; regulatory processes; and degree of 'openness'/collaboration.

Scientific challenges

There was near-unanimous agreement that industry is facing unprecedented levels of scientific difficulty with regards to discovering new antibacterials. This is further compounded by the fact that there is a brain drain away from antibacterials both in the private and the public sector. Many companies have closed their antibacterial R&D units and shifted personnel towards other therapeutic areas. There is an urgent need to ensure knowledge is not lost, but rather captured and made

[4] TATFAR has recently published its recommendations for future collaboration between the EU and the US. The report is available for download at: http://ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/Pages/index.aspx?MasterPage=1

accessible. Moreover, research is being conducted in silos, both in and between companies, with little or no information being pooled for joint research. This is resulting in missed opportunities and chances to learn from others and their mistakes. The urgency of collaborative work between and within 'big pharma', SMEs, and academia was stressed.

Commercial environment
Any successful model of antibacterial R&D should address how to de-link the sales volume of resulting products from financial returns in order to slow the development of resistance. This concern has been articulated by NGOs, governments and industry, including EFPIA, and requires a solution that provides sufficient commercial incentive, while ensuring efficient use of antibacterial resources. While participants agreed on the challenge, no clear or easy way to meet this challenge was identified.

Stewardship
Related to the last point is the importance of stewardship, not only to address inappropriate and excess use, but also to ensure appropriate use, especially in developing countries. The degree to which it is possible and desirable to propose solutions in different markets was the subject of some discussion. Many participants at the roundtable argued that the EU would be better off addressing the issue within its borders. Others argued that the need for antibacterials and the spread of resistance make the issue a global one on which the EU can and should take the lead. The role of diagnostics as a means of promoting appropriate use and avoiding resistance was also discussed. It was acknowledged that diagnostics are also subject to commercial constraints and the use of "prizes" to incentivise diagnostic R&D to assist in tackling antibacterial resistance was also highlighted. The importance of applying stewardship policies in the EU to generics as well as to on-patent antibacterials was discussed, as was the importance of ensuring that stewardship arguments were not used to disguise anticompetitive behaviours. One suggestion about what to do in Europe when antibacterials come off patent was to incorporate a tax on antibacterial therapy, akin to a carbon tax, to raise prices and simultaneously raise money that could be used to support further antibacterial R&D and/or stewardship education programmes. There was some recognition that stewardship is made harder by increased competition among suppliers, adding to the challenge of patent expiration.

Market signals
Companies and payers respond to market signals. Higher prices in high income countries might permit reduced use while maintaining returns and limiting the build-up of resistance, and would also send appropriate market signals to companies about what third party payers want and what they are prepared to pay for. The use of price as a stewardship mechanism, i.e., rewarding companies for conserving resources, is controversial and challenging in terms of implementation. It is likely to be more acceptable in markets with either a socialised healthcare system or one with comprehensive health insurance coverage. Even if this mechanism was to be accepted, both HTA and P&R processes for antibacterials would need to reflect an agreed definition of the social value of a new antibacterial. This would be likely to require collaboration across the EU at the Member State level and between mechanisms in Member State HTAs, e.g. by including restrictions on use as part of their appraisal process.

A more radical proposal was to separate the purchase from use via a buy-out mechanism. In this scenario, the third party payer says it is prepared to pay a pre-defined amount to buy the rights to the antibacterial, and the responsibility to enforce appropriate use then falls on the health care system, with the producer earning a basic return to cover the cost of production. A variation on this was pre-defined price-volume agreements that reduce the rewards from increasing volumes. These ideas are similar to OHE's second recommendation for some sort of "prize" discussed above (OHE were suggesting an AMC or Transferable IP rather than a buyout).

Regulatory process
The regulatory system was also discussed. In particular, the discussion centred on potential reforms that are needed to improve the introduction of novel antibacterials. Although outside the specific remit of the meeting, industry representatives strongly expressed the view that action in this area would have a significant effect on both economic viability and levels of uncertainty. Two areas in particular were highlighted: (i) the challenge of differing and inconsistent regulatory requirements for antibacterials around the world and (ii) the case for reorganising the development and regulatory processes in this therapy area. On the former, having differing regulatory requirements, especially between the EU and the US, entails running more costly development programmes. Evidence requirements by the EMA and FDA can differ from each other and are not always predictable by companies. Thus, there is an opportunity for cooperation between the two agencies to streamline and make these regulatory processes more consistent to reduce these costs.

Of particular concern for industry are the current development and regulatory process at Phase III[5]. One suggestion was to eliminate Phase III trials for new antibacterials altogether, allowing companies to bring them to market after Phase II[6], while increasing evidence gathering post-launch, either via additional "confirmatory" trials or post-marketing surveillance. It

[5] Phase III trials fully establish efficacy and help determine the best way to use a drug.
[6] Phase II trials usually involve several hundred of patients to evaluate safety, determine the best dose and gain early insights into the efficacy.

was noted that there are parallels with other therapeutic areas, especially in terms of early access to new treatments in oncology, and it is important to learn from these experiences.

Degree of 'openness'/collaboration
There was much discussion about the possible role that open source or, more generally, an "expansion of the pre-competitive space" could play in helping overcome some of the early scientific hurdles, especially in light of the success in other industries such as the medical devices industry and the IT industry. The Structural Genomic Consortium (SGC) was highlighted as an example of a successful venture which brought together industry, ex-industry, and academia. The SGC argues that it is possible to expand the pre-competitive space into Phase IIb[7].

Such early stage collaboration could also solve the problem of working in silos and not sharing information. In particular, there are useful lessons to be learned from past failures and successes, not only to avoid duplication of work and effort, but also to use this information on which to build.

Participants had an opportunity to share information about existing collaborative and joint-programming efforts already taking place, as well as funding opportunities for early stage research. Everyone agreed that a mapping exercise would be useful to help capture the current state of play and knowledge.

Final Remarks

There is political and public momentum around the issue of resistance and the lack of new antibacterials in the pipeline. Moreover, there is a need to move forward rapidly. A strong incentive based on the traditional model could be a good way to reignite R&D in the short run and possibly buy some time to allow policy makers to implement policies and incentives that will address some of the more fundamental and systemic problems with antibacterial R&D. EFPIA reiterated the readiness of the pharmaceutical industry not only to play its part in identifying solutions to the problem, but also a willingness to be open to new models of drug development. Specifically, it is eager to engage with the European Commission and other stakeholders to support the Commission's comprehensive action plan, due by the end of this year, with proposals for incentives to develop new antibacterials. It is essential that this happens and that incentives are introduced to make sure that we get new antibacterials, and that their use is managed to prevent the development of more superbugs.

[7] Phase II studies are sometimes divided into Phase IIa and Phase IIb. Phase IIa is specifically designed to assess dosing requirements. Phase IIb is specifically designed to study efficacy.

Annex 1 List of Participants

NAME	ORGANISATION
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