

The Antibiotic Innovation Study:

Expert Voices on A Critical Need

Sophia Tickell, November 2005

The Antibiotic Innovation Study:

Expert Voices on A Critical Need

November 2005

ACKNOWLEDGEMENTS:

This report attempts to capture the findings of a number of detailed interviews with experts in the field of drug discovery and development. As author of the report I take full responsibility for this interpretation and for any mistakes it may contain.

I would like to thank all interviewees for their time, patience and valuable inputs in and outside the interviews. In particular Jeff Edwards, John Turnidge and Tony White gave generously of their time and expertise in this field, as did Lynn Marks who provided vital insights and knowledge.

The report would not have been possible without the active support of the Editorial Board: Professor Otto Cars, Director, Strama; Dr Richard Laing, Medical Officer, Policy and Standards of Medicines, WHO; Dr Anthony So, Director Health and Innovation Program, Duke University; and Niclas Hallstrom, Director, Dag Hammarskjöld Foundation. I would like to thank Otto in particular for always making himself available for comment and insight in spite of a ferociously demanding schedule and multiple other commitments.

Sophia Tickell
November 2005

This study was supported by grants from the European Society of Clinical Microbiology and Infectious Diseases, ESCMID, and The Swedish Foundation for Strategic Research.

Disclaimer:

The Antibiotic Innovation Survey interviewed a broad range of decision-makers and stakeholders in the drug development process. The findings, interpretations, and conclusions expressed herein may not necessarily reflect the views of all the interviewees, who took part in this project in their personal capacity. Whilst based on information believed to be reliable, no guarantee can be given that it is accurate or complete.

Contents

ACRONYMS.....	7	SECTION THREE: THE MEDICAL AND SCIENTIFIC GAP.....	20
EXECUTIVE SUMMARY.....	8	SECTION FOUR: THE REGULATORY ENVIRONMENT.....	23
INTRODUCTION.....	10	SECTION FIVE: THINKING OUTSIDE THE MARKET.....	27
RATIONALE FOR THE PROJECT	11	SECTION SIX: GENERAL CONCLUSIONS.....	29
SECTION ONE: THE FINANCING OF ANTIBIOTIC INNOVATION	15	SUPPORTING REFERENCES	33
SECTION TWO: THE ROLE OF GOVERNMENT IN STIMULATING ANTIBIOTIC R&D	19	APPENDIX ONE – LIST OF INTERVIEWEES	34

Acronyms

CDC	Centre for Disease Control (US)
CEO	Chief Executive Officer
ECDC	European Centre for Disease Control
EMA	European Agency for the Evaluation of Medicinal Products
ESBL	Extended spectrum beta lactamases
FDA	Food and Drug Administration (US)
IP	Intellectual Property
MRC	Medical Research Council (UK)
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NCE	New Chemical Entity
NIH	National Institutes for Health (US)
NPV	Net Present Value
PPP	Public Private Partnership
R&D	Research and Development
SME	Small and Medium Enterprises
TB	Tuberculosis
VRE	Vancomycin-resistant enterococci
VC	Venture Capitalist
WHO	World Health Organisation

Executive summary

The world has woken up to hospital-acquired infections. MRSA regularly makes the headlines, its incidence is monitored and massive efforts are made to control its spread. It is important that this concern is not allowed to obscure an equally worrying reality: the dearth of innovation into new drugs needed to combat resistance. This report is a wake-up call to those who assume that because we have the antibiotics we need today, we will have them tomorrow. It is also a reminder that millions of people across the globe do not even have them today.

The Antibiotic Innovation Study was undertaken to find out why there are so few new antibiotics in the pipeline and to ask experts and decision-makers in the drug development process what might be done to address this problem. All interviewed agree on the need for urgent and concerted action on the part of all stakeholders on the understanding that the prevailing market system cannot solve the problem. The study is not an in-depth research project. However, in presenting the views of senior experts it identifies important areas of analysis and signals where possible solutions might be found.

The structure of the pharmaceuticals market does not provide the right incentives for sufficient investment in antibiotics to meet rapidly changing medical need. Only two new classes

of antibiotics have been discovered in the past thirty years¹. Though new research is being done, much of it builds on existing medicines, and is therefore compromised when tackling resistance.

The consequences, already discernible, are growing numbers of sick and untreatable patients and deaths associated with lack of access to effective antibiotics. The prognosis for five to ten years time is grave. There are a range of unmet medical needs in the antibiotic field that will require different solutions. Treatments are needed for new infections and emerging resistances in developed countries, particularly in the field of Gram negatives. Medicines for community-acquired resistant infections are needed in all markets. And new drugs are needed for diseases that predominantly occur in developing countries, such as TB and typhoid fever. Innovation for these countries needs to tackle both formulation and presentation of the treatment.

Until now in the pharmaceutical industry's main markets, medical need and the need to make profit for shareholders have been broadly aligned. This is no longer the case and antibiotics now risk becoming subject to the same funding difficulties as the neglected diseases that plague developing countries. Historically much antibiotic research has been done by Big Pharma, yet smaller (Biotech) companies with reduced

¹ See footnote ²

infrastructure costs and the ability to accept lower profit margins may prove more suited to antibiotic development. However, they will encounter the same difficulties as Big Pharma in obtaining funds for Phase III clinical trials.

The reasons for antibiotics' relatively poor return on investment are varied and inter-related. First, the most commercially profitable drugs treat the symptoms of chronic diseases. Antibiotics do not make so much money. Second, the pharmaceutical industry has consolidated, leaving fewer people in fewer companies doing antimicrobial research. Third, the science of antibiotic discovery is particularly difficult. Fourth, in a highly genericised market, the overall price antibiotics command is low. Fifth, the push to reduce antibiotic use to prevent the spread of resistance acts as a further disincentive. Sixth, the regulatory environment is increasingly risk averse and is particularly onerous for antibiotics. And finally, given that resistance inevitably develops for all antibiotics over time, the lifespan of these drugs is inherently limited.

In light of the limited commercial potential of antibiotics, interviewees agreed that it is appropriate for government to step in to compensate for market failure. The study did not conclude what the precise nature of government intervention should be, but it did throw up interesting ideas. For some, government should work within existing market structures, investing substantially in early research, removing barriers to innovation, redefining what constitutes value for money in antibiotics and paying more for true innovation. Others favoured a more concerted effort that could amount to some sort of public private partnership. Some argued that the current situation should lead to questions as to how to de-link innovation from end-profit for non-commercial medicines.

Interviewees identified a number of scientific challenges to antibiotic innovation and options that merit further research. Genomics still has great potential but investors and companies need to be more realistic about the complexity of the science and how long it will take to yield results. The development of a public library of rejected chemical substances could facilitate research into promising leads that are not otherwise pursued. Diagnostics could deliver many significant innovations including: a point of care test to differentiate between viral and bacterial infections; improvements in pre-clinical tests for pharmacology and toxicology for early identification of safety problems; the identification and validation of biomarkers; and the development of alternative biological endpoints to complement clinical endpoints. Successful research into a vaccine that specifically targets antibiotic-resistant bacteria could both prevent the spread of resistant infections and reduce antibiotic use and so avoid future resistance.

The regulatory environment is also a vital determinant of antibiotic innovation. Regulations currently come down firmly on the side of risk aversion; a position that could usefully be tested against patient views. The study outlines suggestions on how to remove barriers to innovation in the regulatory process. The whole clinical trial process could be more efficient and amendments made to the rigorous antibiotic trial requirements.

There are various possible means of delivering short cuts on Phase III – the most expensive of all the trial phases – including; improved diagnostics and improving statistical probability measurements. Reducing the number of patients in trials and increasing post-marketing surveillance would help, but the benefits of conditional registration are not straightforward when resistance is factored in.

Of existing tools that help facilitate registration, fast track and priority review already work for antibiotics though speeding up the process further would offer particular benefits to smaller companies and help meet the specific antibiotic needs of developing countries. Orphan drug legislation is not necessarily transferable to antibiotics due to a larger and less predictable patient base and because the costs to health budgets could prove prohibitively high. Nor is Orphan Drug appropriate for developing countries which need cheap and simple first-line therapies.

Increased prices could provide a financial incentive for antibiotic innovation, though reimbursement authorities would need to calculate health budgets differently and be persuaded of the value associated with the increased price. Even if they were, price increases do not address the financial access barriers posed to developing countries and uninsured people, or the fact that health budgets everywhere are under severe strain. The possibility of producing different categories of antibiotics which are priced differently could be considered.

There was unanimous agreement that even if market incentives work for some new antibiotics, other medical needs would still not be met. For some, government intervention should be limited to an injection of capital to support a scouting fund to identify and buy research. For others, government should be involved from start to finish in some sort of formal public private partnership (PPP), including funding early research and advance purchasing agreements. This involvement could facilitate the retention and development of the antimicrobial scientific-knowledge base, currently at risk of being lost.

Despite enthusiasm for intervention, reservations about the transferability of existing PPP models to antibiotics were expressed. Any antibiotic resulting from a PPP could have significant commercial potential in richer markets, making management of intellectual property and discussions about price much more complicated than existing agreements. Interviewees acknowledged that the consolidation of technology and knowledge within the pharmaceutical industry means that many scientists lack expertise on key aspects of translational research. Existing PPPs have not solved the question of how to make the project independent of public funding. Nor should it be assumed that a PPP would be capable of meeting developed and developing country needs simultaneously.

The study concludes that urgent, concerted action is needed by scientists, doctors, pharmacists, governments, the pharmaceutical industry, regulators, purchasers, investors, patients and insurance firms. If not we will be left, in the words of one interviewee *“asking 21st century patients to accept 19th century medicine.”*

Introduction

This report presents the findings of the Antibiotic Innovation Study, undertaken to contribute to the likelihood of bringing innovative, affordable and appropriately used antibiotics to market in the face of growing resistance.

The Study was commissioned by React. React, is an initiative of the Dag Hammarskjöld Foundation, the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents, STRAMA, and the Division of International Health at Karolinska Institutet, IHCAR. Since its inception in May 2004, React has become an independent global initiative and has expanded into a network of practicing physicians, microbiologists, health systems researchers, regulatory authorities, pharmaceutical industry and NGOs working on the issue of antibacterial resistance.

React works to address the problem of antibacterial resistance in three ways:

- a) By communicating the need for urgent action to confront bacterial resistance,
- b) By promoting concerted action to achieve the rational use of antibacterials and to contain antibacterial resistance,
- c) By promoting the development of new antibacterial agents and other technologies to ensure effective treatment of bacterial infections.

The Antibiotic Innovation Study presents the summary conclusions of twenty four interviews with a wide range of experts (see Appendix One) that took place between January and July 2005. Participants, who agreed to be interviewed in a personal capacity, were drawn from the scientific community – both working inside and outside the pharmaceutical industry, academia, the medical profession, reimbursement authorities, pharmaceutical executives from generics, Biotech and ethical/

branded industry, regulatory authorities and experts in Public Private Partnerships (PPPs). All interviewees were asked a number of questions about the decline in antibiotic research and development, the reasons for it, at what point in the drug development process the problem was most manifest and what could be done about it.

This report is a summary of the interview findings. Its value lies in presenting the views of senior, concerned and knowledgeable people about the nature of the problem and what might be taken into account when considering possible solutions. It provides reference for further reading. However, it is not an in-depth research project into how to provide further incentives for antibacterials, nor a comprehensive review of the perceived successes or limitations of alternative models for innovation or existing PPPs.

In some ways, this report has written itself. As far as is possible it is written in the words of the interviewees, indicated in the text by being written in italics. However, it was written with a non-specialist audience in mind, and it therefore outlines key elements of the drug development process. Interviewees took part on the understanding that they would be listed but that their comments would not be directly attributed.

The report is intended as a wake-up call to those who assume that because we have the antibiotics we need today, we will also have them tomorrow. It is also a salutary reminder that millions of people across the globe do not even have them today. Without concerted action on the part of scientists, doctors, pharmacists, governments, the pharmaceutical industry, regulators, purchasers, investors and insurance firms the problem will not be solved, and we will be left, in the words of one interviewee *“asking 21st century patients to accept 19th century medicine.”*

Rationale for the project

“Societal economic benefits cannot enter a firm’s account. It is perfectly consistent for the CEO of a quoted company to disinvest from an antibiotic programme on the basis that the economic benefits won’t come through ... to him and thus to his shareholders.”

“For the past fifty years we have operated on the assumption that drugs equals the pharmaceutical industry equals profit and until recently there has been no other paradigm. Now it’s suddenly dawned on us that there are societal needs that can’t be met by the commercially-driven pharmaceutical industry.”

The Antibiotic Innovation Study was undertaken to find out why, in the face of growing antibiotic resistance, there are so few new antibiotics in the pipeline; and to ask decision-makers and others who influence the drug development process what could be done to address this problem. The project is based on an understanding that existing market structures do not provide the right incentives for sufficient investment in antibiotics to meet rapidly changing medical need.

Ask most people what unmet needs for medicines consist of and they will point to rare tropical diseases, or perhaps to malaria, TB and HIV/AIDS. Few, if any, will think that they refer to treatments for pneumonia, septicaemia, or wound or urinary tract infections. Or to the drugs you need to prevent infection in heart transplants, knee or hip replacements or to complement cancer treatments. Surely, they would think, we have antibiotics to treat these diseases. And for now, they would largely be correct. But look five years down the line and the answer is less clear. Ten years and the outlook is grim. *“Do we need new antibiotics at this moment in time? Probably not,”* says one pharmaceuticals expert. But he adds, *“Will we need them in ten years if trends go the way they are going? Almost definitely.”* And have sufficient numbers of drug manufacturers begun the laborious process of antibiotic development in time to meet the expected growth in medical need? Definitely not: of the antibiotics in late stage development expected to come to market in the next five years there is only one new class² and that is for topical bacterial skin infections (see *Chart One*).

Antibiotics are in some ways the victim of their own success. For many years they were effective, safe, cheap and abundant.

In the past five years, however, resistance to existing antibiotics has become widespread making it imperative to find new classes of effective medicines.

At the moment, society is wholly reliant on market solutions to this problem, yet this may prove a risky strategy, as interviewees from the private sector said, *“The ... market probably won’t solve the problem in time, if you mean will we answer the threat of multi-resistant organisms before significant numbers of people suffer from those infections. There are credible reports of pan-resistant organisms that escape all available chemotherapy and such a patient has a very poor prognosis. I am afraid we will see an increase in the number of such patients before we bring anything to market.”*

“Is the market going to solve the problem of antibiotic innovation? I think in the long run the market will ultimately correct, but I don’t think it will be quick enough. We don’t have that much time.”

The emergence of the “superbugs”, with their fearsome ability to resist antibiotics, is well reported. A new generation is growing up sharing the belief of their great-grandparents and of many people in developing countries, that a visit to the hospital poses a risk to your health. MRSA (Methicillin-resistant *Staphylococcus aureus*) regularly hits the headlines. Other resistant bugs, such as VRE (Vancomycin-resistant enterococci) are not yet household names, but for many doctors, it is only a matter of time.

The extent of antibiotic resistance is not known precisely, and given that it is a moving target, is unlikely ever to be so. Resistance is permanently evolving and gathering evidence is further complicated by the fact that disease collection data does not pick up the role of resistance in morbidity and mortality statistics. *“The area of acute infections has been highly neglected in discussions of the economic downside of poor health, especially those associated with morbidity and mortality, e.g. Meningococcal sepsis, septicaemia, Gram negative diseases. This is partly because the reporting mechanism of ICD10 codes³ doesn’t register resistance and therefore we don’t capture data through our normal medical record system.”* Despite these caveats, surveillance systems do exist and they do provide health authorities with sufficient evidence that antibiotic resistance is an extremely serious and growing problem. Moreover, its spread has increased rapidly in recent years.

² The discovery and development of a truly new class for humans offers the potential of significant advantages in marketing differentiation and in hospital formulary acceptance. The demonstration of clinical advantage is a platform for consequent economic benefits and is a strong encouragement for companies to seek agents that meet these criteria. From a scientific point of view, to be a member of a new class an agent should be able to demonstrate a completely novel/unrelated mode of action associated with a novel chemical structure and therefore be truly free of pre-existing resistance. It should not be affected by any of the mechanisms that affect existing members of the class. Some regulators, on the other hand, appear to be prepared to accept as a new class an agent that is the first in an existing class to be active against a particular pathogen. In this definition, while an agent may be less susceptible to existing resistance mechanisms, it does not have a novel chemical structure that is free of pre-existing resistance. This report uses the scientific definition of what constitutes a new class.

³ ICD10 stands for “International Statistical Classification of Diseases and Related Health Problems – version 10”. This is a set of codes, which translates the written description of a diagnosis into a coded format. This set of codes forms part of an international standard of diagnostic codes and is owned and maintained by World Health Organisation.

Its implications are already apparent. *“The consequences will be seen either in the hospitals, in terms of longer patient stay, increased morbidity-mortality, increased costs, more hospital acquired infections like MRSA and greater difficult in controlling them. In the community, without new antibiotics some of the infections we are seeing in hospitals will emerge in the community... [in both settings] there will be different type of bugs, they will be more pathogenic and more difficult to treat ... The other consequence of course, is ... less incentive, expertise and money for looking at agents to treat organisms of bioterrorism. In developing countries, already stricken with HIV/AIDS, resistance to the commonly available antibacterials will add to the increasingly widespread burden of infection in terms of morbidity, mortality and economic decline.”* Put more simply, *“the outcome of the lack of new agents will be deaths and lots of debilitated people.”*

A WALK THROUGH THE CURRENT RESISTANCE SITUATION

Resistance is not new. Just months after the first mass antibiotic production for use by troops in World War II, resistance to the new wonder-drug penicillin, used to treat *Staphylococcus aureus* (staph) infections, was identified. By the late 1960s 80% of staph bacteria were penicillin-resistant. In 1961 a new antibiotic, methicillin, was introduced to tackle penicillin resistance. Forty years later, according to figures from the US Centre for Disease Control, 57% of staph bacteria were resistant to MRSA (Methicillin-resistant *Staphylococcus aureus*). MRSA is now resistant to many other drugs, but perhaps most alarming are reports of partial, and in 2002 & 2004, total resistance to vancomycin – antibiotic of last resort to treat staph infections – i.e. the treatment used when all else failed. This is an exceptionally infrequent, but worrying development.

Streptococcus pneumoniae is the single most important cause of pneumonia, and the cause of childhood ear infections, meningitis and sinusitis. The US Centre for Disease Control (CDC) recently reported that up to 40% of infections caused by this bacteria are resistant to at least one drug and 15% resistant to three drugs or more. In 2003 in Europe the proportion of penicillin-resistant strep was over 25%, reaching a shocking 53% in France.

Escherichia coli – *E. coli* is often assumed to be a form of food-poisoning. In fact, it is a member of normal human gut flora most frequently responsible for urinary tract infections. It is also associated with peritonitis and is a cause of wound infections. *E. coli* has shown resistance to broad spectrum penicillins and more recently to third generation cephalosporins.

Enterococcus species are responsible for wound, blood, urinary tract, heart and other life-threatening hospital-acquired infections. The core antibiotic treatment for

some species is vancomycin. By 2002 according to CDC in the US, 27% of tested *Enterococcus* samples were vancomycin-resistant. In the same year vancomycin resistance in enterococcal isolates was reported to be above 10% in Ireland, Italy, Greece, Romania and Croatia.

Pseudomonas aeruginosa is a particularly nasty bug that causes urinary tract infections, lung infections, wound and other infections common in intensive care units. One of the most effective antibiotic classes to treat this pathogen is fluoroquinolones. CDC figures of 2002 find that over 33% of tested samples of *P. aeruginosa* are resistant to fluoroquinolones such as ciprofloxacin or ofloxacin.

Tuberculosis, once all but eradicated in Western countries, is making an unwelcome comeback. It is the biggest killer of young people and adults in the world, causing 2-3 million deaths annually, 95% of which are in the developing world. An estimated 50 million people are infected with Multi-drug resistant TB. 80% of MDR TB strains are resistant to three or four first-line drugs. The most recent treatment for TB is over forty years old.

Sources: Bad Bugs: No Drugs, IDSA, July 2004 & Antibacterial Resistance, WHO, Feb 2005

As soon as antibiotics began to be used to treat infection, the disease-causing bacteria began to fight back. They have astonishingly effective and complex survival mechanisms which are constantly changing, requiring scientists to come up with ever-more inventive ways to hit moving targets. The development of resistance is therefore unavoidable. Slowing it down and preventing its unnecessary spread is not.

A first step is to understand and tackle the misuse of antibiotics. Antibiotics are widely over-used in developed countries, particularly in community settings. A common reason for this is the reluctance of patients to leave their doctors' surgery without treatment and of doctors in turn to insist that this is the right course of action. Faced with a feverish child, anxious parents and no way of knowing whether the cause is viral or bacterial, many doctors prescribe antibiotics - just in case. *“We are practicing pretty ancient medicine. There are not many other areas of medicines where you treat before you diagnose. We are dealing with old technology – the agar culture is 120 years old and it still takes 2 days to get a result. It makes eminent sense from a GP point of view to prescribe before you diagnose, but it leaves a rather nasty taste in my mouth.”* Combine this with intense advertising of broad spectrum antibiotics – those that can be used to treat a range of diseases – followed by patient demand and the net result is that of the 80-90% of antibiotic consumption that takes place in the community, over half is considered to be used to treat the wrong thing: viral as opposed to bacterial infections.

In developing countries, the problem is reversed. Cost considerations mean that most people can only access first line

therapies – second and third line treatments are too expensive. Many people can only afford one stab at treatment. If the pathogens are resistant to the medicines they take, patients do not have a second chance. Tight household budgets and very limited government help in paying for medicines encourages people to buy only as many drugs as are strictly necessary to control disease symptoms.

Other things contribute to antibiotic resistance. The extensive and often preventative use of antibiotics in animal husbandry and their use in growth promotion have led to the emergence of resistance in farm animals which can be transmitted to humans through the food chain or via direct contact.

Governments are waking up to the scale and potential consequences of growing antibiotic resistance and a number of national and international programmes are now up and running. Such programmes include surveillance of antibiotic consumption; monitoring of resistance patterns; and advice to prescribers about which medicine to use and when, in order to guarantee appropriate use of antibiotics.⁴ The urgent need for action was endorsed in May 2005 when the World Health Assembly agreed a resolution calling on all Member States to improve the containment of antimicrobial resistance.⁵

However successful these efforts to stem the spread of resistance, new antibiotics will continue to be needed, as one leading antibiotic researcher explains, “Resistance is the key driver for why we will always need new antibiotics for infectious diseases because the target is DNA-based and therefore has the ability to evolve and change over time.”

Antibiotics are divided into classes, determined by what is known as their mechanism of action. Many of the more recent antibiotics that have come to market have been modifications or improvements of the major antibiotic classes that were discovered between 1940 and 1970. These “me-too” drugs may offer therapeutic benefits – fewer side effects, fewer doses – but are a problem from a resistance perspective. The closer a new antibiotic’s mechanism of action is to that of an existing class, the greater the speed and likelihood of emergent resistance. “Antibiotics do not only act on the bacteria you want to treat,” explains an expert in surveillance and control, “but they also modify the ecology (at the site of infection) and increase resistance in other bacteria. As the use of fluoroquinolones, for example, increases, the effect is not seen on strep pneumonia, which is what it is being used for, but instead it is seen on E. coli.”

“There are only some eleven or so major classes of antibacterials and that is not without significance because resistance builds within a class and is now occurring across classes. The main value of a new class is to combat resistance.”

Until now in the pharmaceutical industry’s main markets, medical need for new antibiotics and the need to make profit for shareholders have been more or less aligned. Yet a backward glance at recent antibiotic discoveries and a forward look into what is in the drug companies’ pipelines demonstrate a worrying gap (see Table 1).

Table 1: Antibiotic Launches 2000-2010 NCEs and New Classes

Launch Date ^a	Brand Name (generic name)	Mechanism of Action	New Chemical Entity	New Class ^b
2000	Tequin (gatifloxacin) Zyvox (linezolid)	Quinolone	Yes	No
		Oxazolidinone	Yes	Yes
2001	Spectracef (cefditoren-pivoxil)	Cephalosporin	Yes	No
2002	Invarez (ertapenem)	Carbapenem	Yes	No
2003	Cubicin (daptomycin)	Cyclic lipopeptide	Yes	Yes
2004	Ketek (telithromycin)	Ketolide	Yes	questioned (macrolide-like)
2005	Tygacil (tigecycline) Fimibax (doripenem) T-3811 (desquinolone) Halospor ^c (cefotiam) Ozex (tosufloxacin) Pasil (pazufloxacin) Tazocin (tazobactam) Tomiron (ceftaram pivoxil)	Tetracycline analogue	Yes	questioned
		Carbapenem	Yes	No
		Quinolone	Yes	No
		Cephem	Yes	No
		Quinolone	Yes	No
		Quinolone	Yes	No
		Beta lactamase inhibitor	Yes	No
Cephem	Yes	No		
2006 ^d	retapamulin (275833) dalbavancin	Topical pleuromutilin	Yes	Yes
		Glycopeptide	Yes	No
2007	Sun A0026 (faropenem daloxate) garenoxacin Gracevit (sitaflaxacin hydrate) olamufloxacin (HSR 903)	Carbapenem	Yes	No
		Quinolone	Yes	No
		Quinolone	Yes	No
2008				
2009				
2010				

Source: This table is based on entries in the Lehman Brothers estimates in PharmaPipelines and while indicative of trends, may not be exhaustive.

^a Refers to US or World launch

^b While all agents in this table are NCEs, the majority are chemical modifications within existing classes. They may offer incremental advantage over existing classes, but from a resistance perspective, their utility is limited. For a full explanation of what constitutes a new class, see footnote 2 p.11

^c Italicised antibiotics refer to Japan-only launch

^d Only antibiotics with 50% or more probability to market are included in this table

⁴ The World Health Organisation (WHO) defines appropriate use as “the cost effective use of antibiotics, which maximises clinical therapeutic effect while minimizing both drug-related toxicity and the development of antibiotic resistance.”

⁵ The resolution calls on Member States to develop a coherent, comprehensive and integrated approach to contain resistance, to encourage the appropriate use of antimicrobial agents, and monitor the use of these agents and the level of resistance occurring. It also urges WHO to strengthen its leadership role in containing resistance, to establish surveillance and patient education systems, and to collaborate with relevant programmes and partners to promote the rational use of medicines.

While research continues, particularly into hospital-acquired infections, such as MRSA, investors predict dismal profit potential for antibiotics in the coming years and prospects even for new therapies are at best questionable.

The reasons for this gloomy prognosis are varied. Drug company pipelines across the board are thin, it is not only antibiotics. Yet scientific challenges – compounded by financial and regulatory changes affecting the pharmaceutical industry – militate against antibiotic development particularly. As one industry insider points out, *“One [reason] is the consolidation of the industry. If you look back, thirty years ago there were 30 – 40 companies involved in antibiotic discovery and development. M&A have reduced the number of companies ... dedicated to antibiotics or even one therapeutic class of antibiotic.”* Antibiotics also find it hard to compete on commercial grounds with chronic diseases. A drug that will be used by a patient once a day for the rest of her life offers better commercial prospects than one that is used for a maximum of ten days to treat acute illness. *“Faced with a choice between chronic disease therapy and antibiotics ... the chronic therapy will win out. Antibiotics will find it extremely hard to compete on peak sales figures.”* The antibiotic market is also highly genericised, meaning that expectations of what constitutes a reasonable price to pay are relatively low. Throw resistance into the pot and the incentives fade even further, *“We, the medical profession are part of the problem – we say please rush out and invent new antibiotics, but we want the market to be tiny because antibiotics need to be*

special.” The timing has also been unfortunate. *“The ... upsurge in resistance in the past five years ... coincides with the time the big companies have been getting out of antibiotic research.”* On top of this, the regulatory environment which requires clinical trials for each indication a medicine is used for, is increasingly risk averse. This is particularly onerous for antibiotics.

The Antibiotic Innovation Survey provides a broad brush but important insight into the views of experts as to the reasons for the lack of antibiotic innovation and what can be done about it. The report is divided into six sections. Section One explores how the financial incentive structure for pharmaceutical research and development (R&D) works and why antibiotic development is finding it hard to compete. Section Two argues that in the light of this market failure government needs to play a much more active role in antibiotic innovation. Section Three reviews the scientific challenges and medical gaps in existing antibiotic research and how they might be addressed. Section Four reviews the regulatory environment and proposes interventions that might help ease the passage of promising drugs without compromising standards. Section Five considers that for non-commercial drugs a different approach altogether may be needed and looks at what public intervention might consist of and at the lessons from existing PPPs – both negative and positive. Section Six provides a summary of conclusions covering the key areas of concern and the issues that will need to be addressed by anyone seeking solutions to this urgent problem.

Section One – The Financing of Antibiotic Innovation

“The way calculations are done at the moment there is no way round this. You need between 200 and 500 infectious disease patients for every chronic disease patient to get the revenue, so you’d need a disaster scenario to make acute therapies comparatively profitable.”

Medicines are a social as well as a commercial good. Because of this a great deal of public money is invested in pharmaceutical R&D. A number of successful medicines would not have become available without this input. Nevertheless, under the current model of drug development, the pivotal task of taking drugs through clinical trials, divided into Phases I, II and III (prior to approval) and PIV (post-marketing) is undertaken by the pharmaceutical industry – the private enterprise at the heart of delivering medicines to market.

Pharmaceutical R&D is an expensive business, particularly as development costs often include significant investments in marketing. Quite how expensive is a subject of some debate, but no-one disputes the need for substantial investment to move a compound from being a promising lead to a usable drug, of guaranteed quality, that is effective and safe. The fund managers who make investment decisions have a fiduciary duty to manage money in such a way as to maximise returns on behalf of shareholders. The companies in which they invest must be able to guarantee a competitive return on investment by performing well relative to their competitors in the sector and the sector as a whole must perform well relative to others. During the

1980s and 1990s pharmaceuticals was highly profitable and though this has diminished somewhat, it is still one of the most attractive investment propositions.

The single most important determinant of pharmaceutical R&D is the estimated (discounted) Net Present Value of its future distributable earnings. This calculation is applied to companies and in the pharmaceutical sector, it is applied to therapy areas and individual drugs within a company’s overall portfolio. The most commercially interesting drugs are either first in class (allowing them to capture the market) or best in class. They are also the drugs that are required to keep symptoms under control, rather than preventing or curing the disease. This means of determining how capital is allocated is extremely problematic for antimicrobials which now risk becoming subject to the same difficulties in attracting investment as other neglected disease areas.

RELATIVE ESTIMATED NPV

The reasons for the relatively poor return on investment of antibiotics are varied and inter-related. The first and most cited is that *“the opportunity cost of working in antibiotics as opposed to chronic diseases will always discourage Big Pharma from working there.”* Or as another interviewee put it, when *“faced with a choice between chronic disease therapy and antibiotics ... the chronic therapy will win out. Antibiotics will find it extremely hard to compete on peak sales figures.”*

CONSOLIDATION

The recent period of consolidation in the pharmaceutical industry has exacerbated the problem because fewer people are doing antimicrobial research in fewer companies. During periods of significant restructuring antimicrobial units, which include antibiotics, are often divested from the company (and sometimes spun-off as stand-alone firms). Most of the major pharmaceutical companies have either stopped or down-sized their antibiotic research over the past five years.

SCIENCE IS DIFFICULT

The science of antibiotic discovery is difficult and from an investor perspective, particularly risky (see Section Three). *“The agent must be able to get into the organism in general, not be pumped out of the bacterium, not be degraded by the organism and then be able to attack a system that is critical for the organism’s survival. The microbial diversity is enormous and rapidly evolving.”* Genomics offers interesting possibilities, but from a financial perspective, it still suffers from the fact that initial expectations of how soon it would deliver were unrealistic. Many investors still view the field as too risky, *“The science has become more complicated and difficult and the rewards are not that great – so why bother?”*

PRICE

The third complicating factor for antibiotics is that the price they can command is low. Most antibiotic classes are over twenty years old meaning that their patent protection has expired and generic competition has entered the market. While this makes more medicines available it has a knock-on effect on expectations about what doctors and reimbursement authorities consider to be an acceptable price to charge for new antibiotics. As one interviewee put it, *“I suspect that antibiotic resistance evolved because the basic price is low and because the medicines work – even if only partially... The maximum anyone will ever pay is US\$5 per day for, e.g. a quinolone, and for a maximum of 10 days... Until such a situation as you get complete resistance you will*

not get a proper price comparator. The more genericised antibiotics become, the bigger the problem.”

The Holy Grail for pharmaceutical companies is to have as many blockbuster drugs (with annual sales of more than US\$1bn) in their portfolio as possible. Antibiotics – even innovative ones – enter a crowded market so blockbuster status is unlikely to be achieved through price (see Chart 1).

The other route is via volume, so companies seek to market broad-spectrum treatments that can be used for a number of indications and thereby sold in high volume.

But the growth of resistance has made this difficult. The more antibiotics there are on the market, the more companies have to compete for market share. The introduction of me-too drugs has expanded the overall market. In a vicious circle, this in turn has led to further resistance. In an attempt to halt this process, health authorities argue that new antibiotics should be restricted for use only as treatment of final resort, further diminishing financial incentives. *“We, the medical profession are part of the problem – we say please rush out and invent new antibiotics, but we want the market to be tiny because antibiotics need to be special.”*

To translate reduced consumption into financial incentive the price of restricted use antibiotics would need to be considerably higher than antibiotics usually obtain. Treatments for hospital-acquired infections offer a captured demand that makes this niche possible. *“In theory there is no reason why with an outbreak of MRSA and if you have the only drug that works, you should not make very high return on R&D.”*

And some of the newer antibiotics do, indeed, command higher prices. For this to become more widespread, though, other barriers need to be removed. *“Can pricing be used to the benefit of antibiotics by increasing prices?”* asked one participant. *“For that to happen someone will have to define the value associated with the increased price so that agents are brought to market with reasonable return on investment to the benefit the industry. Someone will have to convince the payers that this is justifiable, which is difficult in a very low priced market.”*

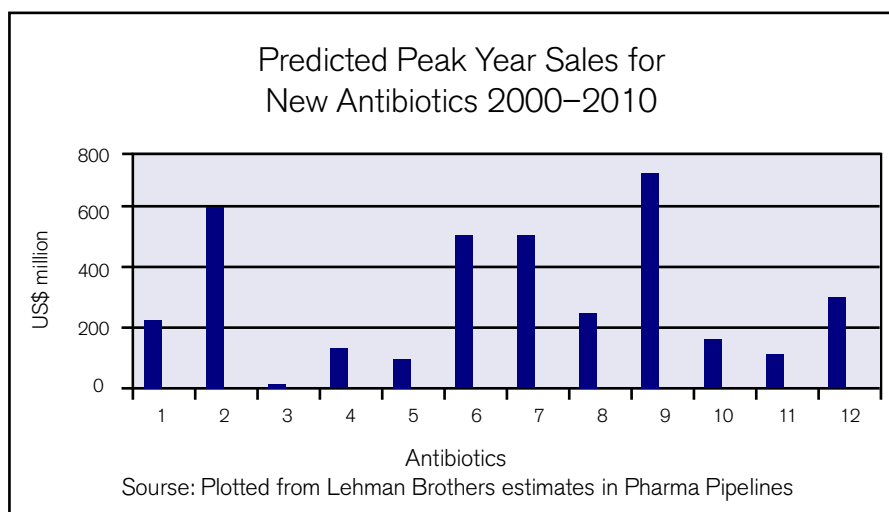


Chart 1

PAYMENT SILOS

Success is not a forgone conclusion. Health budgets are highly departmentalised in almost all healthcare systems, with drugs, consultants' fees, nursing fees, anaesthetics, operations etc., being paid for out of different budgets. This makes it difficult to calculate the relative cost-benefit of using, for example, high-priced prophylactic medicines compared to intensive care treatment in hospital. If calculated in such a way a more expensive antibiotic could still represent an overall cost-saving. *"If there was a holistic approach to cost things could be different. Often the pharmacy budget is quite separate from the patient budget and so the trade offs are never discussed."*

PRICE CONSTRAINTS

Even if such calculations were done, price increases are not universally supported. Discussions about antibiotic incentives take place in an environment of growing unease, particularly in the US, about the increase of medicine prices as a percentage of overall health costs and how this appears to be more to do with what the market will bear than the costs of R&D. As the *Economist* recently put it, *"The more a company can charge for a drug, the more it will spend on developing and marketing it."* Many argue that this situation is unsustainable. *"The cost of medicines, the price that consumers have to pay is getting out of hand. If [price increases] carry on as now, we are simply not going to be able to afford the drugs."*

Even if price hikes for acute use in hospitals were to be accepted, they are unlikely to work for primary care use. While reimbursement authorities may be prepared to accept extremely high, but containable, prices for limited-use medicines in intensive-care settings, they are unlikely to do so for community-acquired infections, where the health budget implications are much harder to predict. *"In terms of NPV the harder part to resolve is when we have resistance to ordinary pneumonia ... I am not sure that there is an easy answer to that."*

Others argue that price increases simply won't work, *"Pricing doesn't reward innovation generally speaking and doesn't dissuade repetition. For a payer to send signals that a drug will only go on the formulary if its cost effectiveness is proved will only work for drugs that are already being made. For drugs that are not desirable those sorts of pricing incentives are not going to be enough of a pull to get companies into an area that they're not already in."*

The net effect of all this has been for the majority of large pharmaceutical companies, the source of much antibiotic innovation to date, to leave the field altogether. As one interviewee puts in, *"the return on investment for antibacterials is a huge challenge for companies and multiple companies have chosen to abandon infectious disease research, especially for antibiotics. In addition to companies leaving there is also a lack of companies entering the field, thus the situation is grave."*

Even where large companies have remained, pressure from investors is such that their continued presence is queried. *"On the question of new antibiotics, I would never be surprised if my*

management called me up to say, "Look, this doesn't make business sense any more." And the justification for staying in is made on grounds, not of demonstrable return on investment, but on intangible value creators for the company. *"The justification to investors is that it is about permission to trade. A drug company operates in a unique space. Everyone thinks governments and National Institutes for Health (NIH) discover drugs and everyone thinks that they are entitled to medicine. They don't really understand that there is a private enterprise playing a pivotal role in the middle. As long as all get what they want things are fine. If the private enterprise loses its sense of its privileged position we are in monumental trouble. The metrics of the financial community pressure all the wrong way."* Intangibles are notoriously hard to quantify. Yet pharmaceutical companies operate in a world in which *"what gets measured gets done."* And what gets measured is financial performance, which is benchmarked against short-term returns, even in industries like pharmaceuticals, with long investment lead times.

DOES SIZE MATTER?

Of course, Big Pharma is not the only player in the field. Some people argue that the cost structure of small and medium enterprises (SMEs) is more appropriate to antibiotic development. *"A smaller company can say we don't need these huge figures to make money. I've heard some say that they would be satisfied with peak year sales of US\$150m. In a big company this would never pass. To be honest, inside Big Pharma people know that the supposed benchmark of US\$500m for peak sales is not even interesting."*

"It is possible to argue that small and medium sized companies might be better placed to articulate need and better able to meet niche [needs] given that they have a business model that includes niche markets as a legitimate way of making money and building the company, especially if the downstream delivery process is done through hospitals or government procurement where there is no extensive need for a sales force."

Others point to *"interesting new sources of innovation such as Indian generic firms who are developing the capacity to innovate."* But generic innovation is not readily accepted in the market place. *"Unless you team up with the Big Boys you won't get accepted in the market – particularly by the prescribing doctors."*

For many, Biotech has both the technical expertise and cost structure to make a success of antibiotic innovation; *"The cost structure of Big Pharma – they will not get out of bed for less than a billion dollars – means there's no point in looking there. They have completely different standards and thresholds. For biotech though, a US\$100m product is a big deal."* *"In a sense Biotech is better placed than Big Pharma to develop antibiotics because they can make sensible economic returns from a smaller product, because they don't have to carry the costs of infrastructure."*

And there is evidence to support these claims. There are more antibiotics in late stage development in small and medium companies than in the pipelines of Big Pharma. The challenge facing these firms is the management of later stages

of development and Phase III in particular. One experienced industry researcher argued, “*Small Pharma, start-ups and Biotechs have the ability to do initial discovery ... but when it comes to development they have neither the experience nor the money to do it. In the absence of advice about how to proceed they don't get anywhere, and most end up wanting to sell out their discoveries or merge. For this early work you need a small budget ... Up to the point of pre-clinical I don't think there is a difference. But once you get beyond that, big firms have the edge with their ability to do in-house tox[icity] studies and clinical studies.*”

“There is a question as to whether biotech has the resources to introduce a significant new medicine. PIII trials are so expensive, which makes it very difficult for an average-size Biotech company to get through with home grown product. Two US companies have got an in-licensed compound through trials showing that small products without back expenditure on research are viable. But it was a struggle and both had to reshape their companies in order to match financial demand.”

Another cautioned against this conclusion, pointing out that much trial work is now contracted out by Big Pharma to Contract Research Organisations (CROs) and there is no reason for Biotech not do the same⁶, “*The belief that Biotech is good at research but not development, is true in general but is often false in the specific. Though it may be generally true that Biotech lacks regulatory or trial expertise, in specifics, the old model, or a hybrid of it, can work. Of course, it will depend area by area. There is probably still a pathway to get through in the existing system but it does require the vision of one group of scientists who have gone and got the money.*”

Another pointed to the fact that the relationship between Big Pharma and Biotech is, in fact, increasingly symbiotic.

“A few years ago big companies were interested in biotech products for licensing. Now it has switched and Biotech is asking Big Pharma what they've got for them. They need molecules in their pipeline to attract the investment. Big Pharma might want to do a deal to get research into molecules that due to time span, technical hurdles or commercial considerations wouldn't be priorities for in-house development. Pharma then permits out-licensing to the Biotech, which then overcomes technical hurdles before it is brought back to Big Pharma for clinical development and registration.”

One logical way to tackle the problem is to create an antibacterials unit as a separate part of an existing company or as a stand-alone company. Indeed, a number of the new Biotech firms are spin-offs of the antimicrobials divisions of Big Pharma companies. Such a unit could be a mixture of PPP on the one hand, for those bacterial infections that are really rare and are not going to provide a good return on investment, and commercial on the other, to generate funds to sustain the whole of the business. This could be run on a cost-neutral basis as some tropical diseases work already is. However, it raises questions about the acceptability of cross-subsidising non-commercial drugs with profits from commercial drugs and does not take into account that much antibiotic research is directed at broad spectrum treatments able to treat more than one disease.

Whatever the theory about the best structure, the stark fact is that there are only a handful of new antibiotics in the combined pipelines of all these players. Only two new classes have been discovered in the past thirty years. Of the fourteen antibiotics expected to be launched between 2005-2010 all but one are additions to existing classes (see Table One).

⁶ Contract research organizations (CROs), now control approximately 70% of the outsourcing market. It is estimated that there are approximately 1,000 CROs worldwide and that they are involved in as many as two-thirds of clinical projects (See Supporting References)

Section Two: The Role of Government in Stimulating Antibiotic R&D

“If we have a situation where pharma is not bringing drugs to market, either because they’re not looking or because they’re not there, we have to have government intervention.”

The financial incentives are insufficient, the science particularly demanding and yet the medical need is growing. In these circumstances all those interviewed agreed that government should take action to address market failure. *“If you find when you have adequate information that the given price points of a particular drug mean it is unlikely to be a commercial proposition, when we know that when the market mechanism fails to deliver on a social good, then that’s where government should intervene.”*

“Is the market going to solve the problem of antibiotic innovation? I think in the long run the market will ultimately correct, but I don’t think it will be quick enough. We don’t have that much time. If I was the government I’d bring in (the companies) still in antibiotics, plus two or three of the hot Biotech, and say we’re worried, 15,000 a year are dying and ask what they are going to do about it. Government has to be clear about what it wants. I think there should be a government, regulatory and academic discussion about what is needed and what the risks are. . . . Governments need to articulate what they are prepared to accept.”

“To address the problem we need a strong [political] leader. Most researchers and politicians want to invest in the here and now,

something that they can point to and take credit for. Very few argue in terms of long-term scenarios – except of course in the case of bio-terrorism.”

“The public sector should take the lead on this subject, though it should not be in charge of all R&D steps. In terms of defining priorities and selecting candidates the public sector should take the lead.”

It was not within the remit of this study to come to precise conclusions about the nature of government support for antibiotic innovation. A more detailed review is needed. Nevertheless the Study did throw up interesting ideas that could help frame such a review. For some, government should play a role within the existing market structures, by investing substantially in early research, by removing barriers to innovation and by redefining what constitutes value for money in antibiotics and consequently paying more for true innovation. Others were in favour of a more concerted, government-convened effort that would amount to some sort of public private partnership which might provide the opportunity to review how to de-link innovation from end-profit for non-commercial medicines.

The next two sections of the report outline the obstacles to antibiotic innovation throughout the research and development process and identify possible solutions, both market-based and public interventions.

Section Three – The Medical and Scientific Gap

“It’s one of the oddities of life that as the knowledge of life-sciences grows the numbers of drugs that comes to market declines. There’s an odd sort of law that has operated there. It should be the other way round.”

Use of antibacterial drugs over the last 60 years has triggered a combination of genetic and biochemical mechanisms within the bacteria to secure their survival in environments where antibiotics are present. Bacterial clones with natural and acquired resistance have continuously been selected as an evolutionary response to the use of antibiotics. Resistance can be acquired as a result of genetic events causing alterations in the pre-existing bacterial genome such as point mutations and gene amplifications. The other major mechanism is horizontal gene transfer between bacteria both within and between species, where transposons, integrons or plasmids are introduced into an organism. The introduction of new antibiotics has resulted in accumulation of genetic elements coding for resistance mechanisms that can be transferred between microbes and create clones with multiresistant properties. The genetic alterations in bacteria cause resistance to antibiotics in one or more of four principal ways: the target molecules are structurally altered to prevent antibiotic binding; antibiotics are excluded from cell entry; they are inactivated, e.g. through enzymatic degradation; or they are pumped out of the cell (efflux).

THE GAPS THAT NEED FILLING

The early science of drug development starts with the identification of targets, the molecules in the body that may be

addressed by drugs to produce a therapeutic effect. Identification of targets is done by screening agents in chemical libraries against target diseases or by applying knowledge of molecular biology to achieve a better understanding of the structures, functions and interactions of genes, proteins and cells. Using this information, researchers select compounds for screening, or sometimes design synthetic compounds for a specific target. This early research is undertaken in universities and government research laboratories as well as inside private companies.

Antibiotic research is particularly complex as one scientist explains, *“the ...agent must be able to get into the organism in general, not be pumped out of the bacteria, not be degraded by the organism and then be able to attack a system that is critical for the organism’s survival. The microbial diversity is enormous and rapidly evolving.”*

THE MEDICAL NEED

There are a range of unmet medical needs in the antibiotic field that will require different solutions. In industrialised country markets treatments are needed for new infections and emerging resistances, particularly in the field of Gram negatives. Treatments for community-acquired resistant infections are needed in all markets; and in developing countries treatments are needed for resistant TB, typhoid fever and gonorrhoea. In these countries it is vital to simultaneously tackle the issue of antibiotic misuse.

The spread of antibiotic resistance creates a constantly changing landscape requiring continued and committed research, *“Most*

[antibiotics] are now exhausted: Lactams have long been considered very safe, yet in some recent examples, new toxicities were seen; Quinolones are also running into difficulties and numerous examples in development have been terminated and two which were launched have been withdrawn.”

“Antibacterials pose different challenges to other therapies. There are multiple targets for multiple bugs and also changing targets because of resistance... You also need to realise that completely different structures are needed for community and hospital.”

GRAM NEGATIVES

It is theoretically possible that some acute medical needs in niche areas of the market may be met within existing structures – in particular treatments for high end of the market products to treat life-threatening conditions. Research is being done, for example, on serious hospital infections, MRSA and vancomycin resistant staph. However, there is widespread concern about the lack of successful research into Gram negative pathogens. *In some areas, Gram negatives, for example, we are very short of time.” “Pseudomonas aeruginosa bacteria which are resistant to fluoroquinolones is a serious problem”. “ESBLs - extended spectrum beta lactamases – a different type of Gram negative organism resistant to all common antibiotics for urinary tract infections, is making patients vulnerable to septicemia”. The “revival of the use of colistin which is now being used to treat multi-drug resistant Gram negatives” illustrates the depth of the problem. Colistin “was discovered in 1949 but later abandoned on grounds of neurotoxicity.”*

In primary care, a critical, yet likely to be unmet need, are treatments to tackle Gram negatives that are more common in the community and currently picking up resistance to existing antibiotics. *E.coli. ... “is a growing concern.” “E. coli, which would normally be treatable by oral antibiotics, is picking up resistance to penicillins and [third generation] cephalosporins.” “Early indications of resistance to third line treatment in carbapenems is very worrying.”*

The needs of developing and developed countries differ. For the majority of people in developing countries cost considerations rule out all but first line treatment. Therefore this first line treatment for multi-drug resistance cases has to be very sophisticated and *“to encompass both formulation and presentation of treatment.”* The best overall solution would be prevention, possibly in the form of vaccines. In their absence, *“if antibiotics are to be effective in developing countries they need to be very simple to use and very robust... The best solution is a one shot, long-acting antibiotic, preferably oral.”*

EARLY RESEARCH

In the light of the limited financial incentives (see Section One), many looked to government to tackle the problem, *“We need a massive injection of government funding at the research phase.” “There is not enough government funding for academia.”* However, for many it should not be unconditional. If public

money is available *“there needs to be a sense of where is it going and why and how will it help to bring in new antibacterials and does that feed into industry efforts? Most of the research projects ask for industry to be partners, but in practice it doesn’t mean much. These are academic projects and I am not sure to what extent industry is involved in the design or what comes out at the end of the day and its utility.”*

THE SCIENTIFIC GAPS ENOUGH TARGETS?

There was disagreement among the interviewees about whether enough targets are being developed. Some clearly do not think so. *“There is not enough coming through and that’s the top and bottom of it... In my view, the biggest impediment to development is that there are not enough targets to begin with.”*

Untapped research may exist but not see the light of day, *“I am convinced that there are many targets that have not been found. I travel a lot and people say ... I have something, but I don’t want to go to industry because they will steal it from me. I don’t believe we have run out of targets, but the method we use – high throughput screening – is not very successful at finding new drugs, including antibiotics.”*

Others do not consider a lack of targets to be the problem. *“My understanding is that we are not short of targets. [But] they have not been successful in matching molecules to hitting those targets and coming up with viable leads. I’ve heard that genomics has delivered the targets and what’s been the failure has been the development of molecules to hit the targets.”*

The other areas of science mentioned as being ripe for further exploration were *“the problem of latency and the persistence of dormant infections... The science of latency is very underdeveloped”* and *“the combination of old and new antibiotics, i.e. combining old ones to overcome resistance. But this is problem of science and a problem for regulators.”*

THE PROMISE OF GENOMICS

The science of genomics still offers great potential that past disappointments should not be allowed to overshadow. *“The potential of genomics was radically oversold, the timing misunderstood and people moved out prematurely. There needs to be much greater effort on genomics-based research.”*

“I think the key failure in our area – antibiotics – has been the difficulty that the pharma industry has had in using genomic innovation to have a significant impact on drug discovery. There was a huge expectation in the early days that there would be a flood of new targets – [we have been] moderately successful in tools but not in delivering innovative targets.”

“There is still a lot that can be done with genomics. Genomic tools are still being refined; proteome analysis and transcriptome analysis that tell you about the mechanisms of actions of new compounds – this is a growing field that’s becoming more accessible to academia

and which will be very useful in a few years time. By then we'll have a very good understanding of the physiology of bacteria. So there is hope for new targets."

"I think there is a blur now between what was genomics and genomic-derived targets and what is coming from looking at bacterial physiology textbooks. But there are new targets that wouldn't have been tackled without the benefits of the genomics analysis."

But for this to yield fruit, investors and companies need to be more realistic, *"what people need to understand in genomic research is that typically speaking, once you find an essential gene you need to go through up to 20 stages before you can begin to assess it as you would a normal white powder. You can fall at any hurdle. Many turn up a very small number of targets and focus down on them inadvisably (it's all they have)... I've known many companies who've rushed in enthusiastically, focused too quickly and then given up too early."*

Whether there are enough targets or not, their subsequent development remains the core issue. As is explained further in Section One, *"The principle impediments to new targets being developed remain finance and time."*

"Loads of targets have been identified and the genome has now been sequenced. What is not known is whether they are druggable. One impediment is probably the retention of IP [for] a drug ... which companies have no commercial interest in making available. So drugs are not created against those targets, but the IP is not wasting. What is maybe wasted is the opportunity for drugs to be in the public domain. But if nothing developed then from the firm's perspective nothing is being lost."

A PUBLIC LIBRARY?

This area could usefully be explored further. *"Some say that potential products are put in the drawers at an early stage. These could be made available. A public library of rejected chemical substances could be set up and made widely available to anyone able and willing to develop them. The criteria for eligibility would be some sort of public guarantee of use."*

Something like this is beginning to happen. *"One result of the failure of the pharmaceutical industry to develop new products for which there is unmet need is that it is beginning to make academics go back into the business of drug hunting which they stopped doing for 50 years. NIH (National Institutes for Health) and MRC (Medical Research Council) are setting up their own chemical libraries intended to stimulate others into the field of drug hunting."*

Some sort of shared chemical library for antimicrobials would be important to help overcome one of the other problems arising from the concentration on chronic disease therapies. *"The bulk of pharma research is to find chemicals to bind human receptors",* which are not appropriate for antimicrobials. *"With the exception of antibacterials we are looking for the type of molecule that interacts with our cells, human cells. The type of molecule that interacts with that receptor, to influence your asthma, or whatever, is a totally*

different type of chemical from those needed for antibacterials... If most chemicals were synthesized with the mindset of seeking a human receptor interface, they are very unlikely to react against antibacterials. [So there is a] built in bias against bacterial disease."

To address this, one suggestion was to make early scientific discoveries open source. *"You could get a whole bunch of people working together in their spare time and put any early stage discovery into the public domain. It won't bring you a drug to market, but it may give you new exciting novel mechanisms for tackling bacteria."*

DIAGNOSTICS

One area of scientific research that could make a huge difference in the field of antibiotics is diagnostics. *"What is needed is a point of care test. Broad spectrum antibiotics are applied in the absence of efficient testing. The reading technology exists, but whether it's sophisticated enough to get this kind of result, I'm not sure. These tests ... won't be cheap, but it must be possible to get machines to automate the process."*

Another use for diagnostics was also identified, *"You have people who survive extraordinary things and their blood is worth US\$1,000 a pint for the first two weeks after survival, because it can tell you so much... I think it is more likely that diagnostics will be used for [this] than for prescribing purposes."*

However, this is easier said than done, *"Finding the exact causative bacteria of an infection is far more difficult to do than is appreciated by most people."*

"Improved diagnostics would be helpful for the entire field but these have been slow to be adopted in the field. Expense, turnaround time and the [liability] implications of inaccurate test results are all impediments to the uptake in the management of infectious diseases. This is slowly changing and has the potential to help with clinical research. We have employed diagnostics to aid in some of antibacterial clinical studies and certainly the ability to use viral load as a surrogate in HIV clinical research has made a tremendous impact on our R&D ability so I am optimistic that new tools for antibacterials could also enhance productivity. I just don't see them in the immediate future."

VACCINES

There is no vaccine that specifically targets antibiotic-resistant bacteria. However, such a vaccine could prevent the spread of resistant infections, thus reducing antibiotic use and so avoid future resistance. Although any vaccine for resistant strains would have to be very specific, the development of the meningitis vaccine was described as providing important lessons which might be applicable to support vaccine development in the antibiotic field. In particular government guarantee of the final market was considered important to the success of the project. The speed with which government has responded to the need for a vaccine for the potential pandemic spread of a human variant of avian flu also sets an encouraging precedent.

Section Four – The Regulatory Environment

No medicine is 100 percent safe. Society has become very risk averse fuelled by developments in the legal climate and a public that assumes that medicines have to be totally safe. Regulators are now very cautious in their approach. We need a paradigm shift in risk aversion and a better way of predicting which patients will have problems with a compound.”

Once basic research has translated a promising lead into a potential drug candidate, its properties are then studied in animals and cell cultures. Only a tiny proportion of the candidates that enter this pre-clinical development phase go on to be tested in humans. To ensure that the final product meets requirements for quality, efficacy and safety this period of clinical trials is highly regulated.⁷Antibiotics are no exception and given the considerable existing difficulties of competing with other therapies, a review of possible barriers to innovation within the regulatory structure is necessary.

NORMATIVE REGULATORY ENVIRONMENT: RISK AVERSION

Prevailing social norms about what is an acceptable risk-benefit equation dictate the extent of information required, including toxicology tests, dosage, time requirements and number of patients in clinical trials. Regulations currently come down

firmly on the side of risk aversion. *“We have ourselves locked into a paradigm of drug development that...has become more and more burdensome. There is no effort to find out whether we’re getting value for money. The pharma industry is to some extent to blame because they’ve never fought against this. They’ve gone along with what the regulators require. Regulators are risk averse and demand more and more data and pharma is prepared to pay the price in order to keep out the small boys.”*

Regulators respond to the signals they receive about what is acceptable. The regulators *“do constitute a bottle neck – requirements are definitely higher than they use to be, but that is because society wants drugs to meet certain criteria. If we diminished the requirements of safety, efficacy and quality it would make drug development cheaper. But no-one wants that.”*

And they base their information on hard data, *“Regulators ... don’t make arbitrary rules. Requirements are a result of academic input. If the science changes it could open up possibilities for requiring less data. In recent guidance [regulators] have tried to convey a new message about increased flexibility. We can take short-cuts as long as they are science-driven.”*

Some argue that the net should be spread wider to given patients themselves a better chance to say what risks they are prepared to take. *“The thing we lack is a patient perspective. Regulators are frightened to do it because they’ll get a bad press, but we badly need*

⁷ **Phase I:** Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients.

Phase II: Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.

Phase III: Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling.

Phase IV: Post-marketing studies to delineate additional information including the drug’s risks, benefits, and optimal use.

Source National Institutes for Health, US Government

a better system to develop a patient position, to really hear what they have to say. It's no good getting a couple of patient advocacy groups. You need a representative group of patients who have the disease and express their views about whether they are prepared to take the risks. It's not helped by the relationship between industry and patient groups and the current mistrust. Is it a buyers group, has it all been bought by the companies?"

Such views should be sought in all markets. *"It is a question of risk-benefit analysis, particularly on toxicity profile. Today many people are still dying from diarrhoea in Africa – you need simple, effective treatment even if there are side effects. We are very risk averse, and perhaps we should be willing to accept more side effects in exchange for better medicines for developing countries."*

It is important that regulation is not blamed for what are commercial decisions, *"The problem is that industry has decided not to develop drugs and is blaming the regulators."*

PRE-CLINICAL

There was strong support for improving the predictive value of pre-clinical findings, *"[Evidence] is largely anecdotal at the moment. The regulatory authorities are the only people who have the data we need. They need to go back over the past thirty years to look at the things that caused problems in humans and the things that didn't, what do the animal studies show... Were they of any predictive value, and if so how?"*

"Predictability of pre-clinical tests for pharmacology and toxicology needs to improve so development of compounds with potential safety problems is discontinued as early as possible to minimise both the risk and the spending. In the period from 1992 to 2002 global spending on medicines R&D grew from US\$25bn to nearly US\$50bn while the number of innovative new medicines decreased from 45 to 28, so productivity is declining. We need to be able to identify patients who should be prescribed a specific treatment using biomarkers and those that should not have a particular treatment due to risk of adverse reactions. There have been developments in hepatic/liver iso-enzyme diagnostics to identify more readily how people will react or metabolise medicines. Physicians need much better diagnostics – biochemical and others."

BETTER DIAGNOSTICS

"Improved diagnostics could work if you had a quick diagnosis of a specific group of pathogens that your antibiotics would be effective against. If you could use that to select patients it would allow PII and PIII to be shortened because it would allow you to identify the right patients for the trials." Likewise, *"pharmacokinetics and pharmacodynamics offer a potential shortcut for the number of patients by improving predictive cure rates. Test-tube and animal models could be tested against pharmacokinetic data to predict accuracy and reduce patient numbers."*

TOXICITY

The regulatory environment and attitudes to risk are very important for antibiotic development. *"Far higher levels of antibacterials are required in the human blood stream compared to agents targeting human receptors and this creates a major hurdle in terms of finding antibiotics safe enough to be tested in humans."*

Much better readings are now available, *"There are other advances militating against antibiotics and in particular two developments at the FDA. The first is an enhanced ability to identify liver toxicity and the second is the ability to measure extension in the QT interval – electrical activity in the heart. Many quinolones and macrolides seem to have had an impact on the QT interval."* Yet, the value of the information is questioned, *"The science base for the studies we do is non-existent. No-one has sat down to ask whether the funny little cells you get with some drugs in the liver really do represent a risk to human beings."*

"To look into new principles for antibiotics requires identification of new methods of action... In the medicines development process there are a number of important bottlenecks, e.g. in the fields of predictive pharmacology and toxicity and identification and validation of biomarkers. New ways of delivering medicines including antibiotics could be achieved by means of nanotechnology to get the active substance into the bacteria."

REMOVING BARRIERS TO INNOVATION IN THE REGULATORY PROCESS

The whole clinical trial process could be more efficient, *"Phases I-III are currently done in an extraordinarily unproductive mode. We do the PI studies then we think about it for a year. Then we do a PII trial or a couple of PII trials and think about the results of that for a year. The whole thing should be seamless. PI should lead seamlessly into PII and then seamlessly into PIII. Even the terminology is a bit crazy. The minute we have an inkling that it might be effective we should be moving into a much wider patient population."*

Even if the process were more efficient, it would be important to assess whether improvements could be made to the particularly rigorous trial requirements for antibiotics. These arise because companies seek to market the medicine as widely as possible, meaning each indication has to be tested, and because resistance has evolved, in some cases companies are required to prove not only efficiency but also superiority. For some the requirements are now too onerous to be efficient, *"What I do know is that we don't half 'over egg the pudding' when it comes to licensing antibiotics. For each indication (e.g. lower urinary tract, upper urinary tract, lower respiratory tract, and so forth) each has to have own clinical trial. For antibiotics that's probably crazy, because it's the one thing where you know that if you're getting the right concentrations you can be pretty sure about what infections it will treat. I'm told you now need 8 or 9,000 patients to get a new antibiotic licensed which is completely ridiculous."*

“The issues are a) the number of studies you have to do - agencies want more information and more specific indications, b) The other issue is endpoints and delta measurements – they are now looking at delta⁸ of 10%, increasing the number of patients to show equivalence to an existing agent, and, c) – comparative trials, and not just comparative trials to show your agent is not inferior – for some infections agencies now want demonstrations of superiority.”

Antibiotics have also to prove efficacy against resistant organisms which is difficult, *“because there are so few around, particularly in the clinical trial populations. It can take you years to get enough data.”* Again, the desire to slow resistance and commercial pressures clash, *“Companies want to be able to show effectiveness against resistant bacteria because that is a differentiator, but they don’t want that to be the only indication on their label.”*

For small companies, the first bite of regulatory costs is felt at Phase I. *“We have been talking to one or two [small] companies and they already say that toxicology studies to satisfy regulatory requirements in Phase I are more than they can consider, so they are looking to partner their compounds in Phase I. This makes for good partnering prospects for Big Pharma because they are relatively cheap, but for Biotech it doesn’t bring in much revenue to the company... The bigger the company the later they are forced to meet that hurdle which forces them to partner and lose their internal cost advantage. So changes that would ease the regulatory process without compromising standards would help bring more compounds through.”* One such change could be to improve *“predictability based on preclinical tests ... making it possible to skip or minimise PI and move directly to patients like, for example, in cancer. Today many PI studies are done because it is a regulatory requirement, but not because there is any real clinical need.”* Likewise at Phase II, antibacterials differ from other therapies. *“For antibacterials there has always been a debate about whether PII is necessary at all ... Now people are looking for a finer balance between enough for efficacy and as low as possible for tolerability and safety.”*

However, it is at Phase III – the most expensive of all the trial phases – that many feel the changes need to be made. *“There are two things that could be done to deliver possible shortcuts: First, can we reduce the number of patients exposed and second, can we invest more in post-marketing surveillance? The big issues in antibiotics recently have only emerged in post-marketing surveillance. You can’t confidently measure risk until the number of people exposed reaches more than 100,000 which is way beyond the requirements of Phase III.”*

FAST TRACK REGISTRATION AND PRIORITY REVIEW

Fast Track registration and priority review procedures that speed up the process of bringing a drug to market are already available in both Europe and in the US. The first glycylicline was approved in the six month period to June 2004. This is a tetracycline analogue. However, interestingly, it was defined

as a new class apparently on the basis that the drug was the first in its class to be able to treat a particular pathogen, rather than because it was able to demonstrate a completely novel/unrelated mode of action associated with a novel chemical structure (see footnote ¹). Providing SMEs with support to use these procedures appears to have the potential to increase their capacity to bring innovation to market. *“Antibiotics ... have different requirements to other therapies. Big companies are better at large scale clinical trials ... complicated regulatory requirements, large scale manufacture, marketing and integration. However, for restricted use antibiotics none of these advantages is necessary. What you do require is a small company able to produce the science at a much lower cost, which is then provided with additional support to get through clinical development. This will include support with regulatory requirements, access to fast track procedures, and information about what is needed in trials and so on. There is a very strong correlation between scientific support from regulatory authorities ... and success.”* *“Anything that can speed up the review process to cut timelines would help smaller companies. The key to this would be more staff in the reviewing bodies. I know for example, that the FDA has so many things to look at that you are often just waiting for a slot for them to look at you.”*

Fast Track could also help with the specific need for antibiotics in the South. *“In many countries you have very good public research institutions doing clinical studies, some with external support. For example, on malaria, there are plenty of good teams in Asia, Africa and Latin America. Fast-track approvals are essential for developing new antibiotics for the developing world.”*

Orphan Drug legislation is designed to encourage R&D into diseases for which there are inadequate market incentives due to the small number of patients suffering from the disease. It provides additional incentives to those provided by the market, including extended market exclusivity. Though at first glance it appears that Orphan Drug-type legislation could be effective in providing incentives for some hospital-acquired, restricted use, high priced drugs, the lessons from the Orphan Drug experience are not necessarily transferable to antibiotics. Orphan Drugs by definition treat a small number of patients. Due to a potentially much larger (and much less predictable) patient base, there is a danger that the costs to health budgets of extended market exclusivity would be prohibitively high. In addition, the Orphan Drug model *“is entirely inappropriate for developing country settings where the greatest needs are for cheap, simple to use and robust first-line therapies.”*

POST-MARKETING SURVEILLANCE

Post-marketing surveillance of medicines once they are in the market place is currently patchy. Conditional registration – which acknowledges that the predictive value of the registration process is limited and so brings the drug onto the market as early as possible on condition of subsequent data submission – is sometimes used. But its benefits are not straightforward. It is at this stage that companies seek to prove that the medicine can

⁸ The Delta is the minimum clinically important difference to be detected in a clinical trial. It depends on a number of factors including the research hypothesis, patient characteristics, the nature of the intervention and the trial design.

be used in as wide a patient population as possible in order to prepare the way for future marketing and sales. Broad spectrum antibiotics are something of a Holy Grail in this respect. If you are seeking to control resistance, however, the impulse is to keep the labelling narrow. This creates a strong tension. *“Of course you will want to restrict use, but there will be no money in it for industry so how do we work it out?” “If fast-tracking ... certain types of drugs ... reduces labelling or slows down introductions to broader labelling, the result is a reduction on return on investment. If earlier to market means restricted labelling the problem is not necessarily solved.”*

There is an issue about what to do in the case of non-compliance. *“The rules are all there. You can get provisional licenses and manufacturers then have to come back with further data. You have to promise to come back in two years time, but my understanding is that companies almost never come back with the further data and then you're in a mess.”*

Others support the idea of post-marketing surveillance, but question who is best placed to do the monitoring, *“I don't think companies should be doing the surveillance. People are more and more aware that currently surveillance is marketing presented as science, when it should be pure science and clean numbers without interpretation.”* To overcome this problem one *“option is to create a pan-European project for electronic patient records to monitor pharmacovigilance that would permit really good surveillance.”*

IMPROVED STATISTICAL PROBABILITY

Another proposal to improve the efficacy of Phase III argues in favour of using different statistical analyses to calculate probability⁹, *“Almost invariably trials are done as parallel group, double blind (with a comparator in antibiotics) and analysed then in the frequentist approach. That's crazy actually. I think we should use Bayesian statistics, which are largely ignored or forgotten, though there is a resurgence of interest. The thing about Bayesian statistics is that it produces probabilities in different ways. It doesn't have a P value. What you do is to get a frequency distribution – a probability density – and you make a judgment based on that distribution and you can work out 95% credible intervals. But basically it's a subjective approach to probability, to which you apply a probability interval.”*

TAX CREDITS

There are a number of other options that can be used to encourage innovation, but none were advocated in this round of interviews. Although tax credits to incentivise R&D have been effective in the implementation of Orphan drug legislation, it appears that additional pull incentives of a clearly defined market have to be in place for them to work. Thus tax credits alone would be insufficient as incentive.

AN ADVANCE PURCHASE AGREEMENT

Some argued that to meet the dual challenge of resistance (existing and future) and the need for incentives, government and health insurance schemes should come to agreement with industry about an advance purchasing agreement which makes payment independent of volume. Others say that the same goals could be met by ensuring that pricing is more determined by clinical effectiveness giving industry and price-setting bodies greater certainty. The development of the meningitis vaccine was described as a success story in which government guarantee of the final market played a critical role. There are also valuable lessons about the pros and cons of advance purchasing on other vaccines, and of growing evidence that the widespread use of vaccines is increasingly linked to a decline in resistance.

Others took the view that the end market is so fragmented that coming to an agreement would simply be too complicated. However, there may be significant differences between the US and Europe in this regard due to the differences in reimbursement structures and the fact that the government is such an important purchaser of medicines in Europe.

TRANSFERABLE INTELLECTUAL PROPERTY RIGHTS

The proposal under Bioshield II¹⁰ for Wild Card IP provision, whereby companies are allowed to transfer patent rights from a less to a more profitable product, was acknowledged in interviews. However, no-one proposed this as appropriate for the development of new antibiotics.

⁹ Clinical trials involve testing a new treatment against either placebo or an active comparator. Most are undertaken using a “frequentist” statistical approach which determines the P value, the probability that any difference between two treatments has arisen by chance. It has been argued that this results in an overemphasis on hypothetical testing and the inferences drawn from P values, and alternatives have been proposed (See Supporting References).

¹⁰ Project BioShield was approved by US President Bush 2003 “to accelerate the process of research, development, purchase, and availability of effective countermeasures against agents of bioterror.” BioShield II, an extension of the Act, is under consideration.

Section Five: Thinking Outside the Market

Even if a package of incentives were successful in promoting innovation for some new antibiotics, there was unanimous agreement that some medical needs would not be met. These included: new infections and resistances in both developed and developing country settings – particularly in the field of Gram negatives; and existing resistant diseases in developing countries – such as TB, gonorrhoea and typhoid fever. In this instance, interviewees all agreed on the need for some sort of more assertive public intervention or a more formal PPP to meet the need for antibiotic innovation. Though what it would consist of was not clearly defined, there was strong enthusiasm for some sort of public-private initiative in the face of this market failure.

A fully not-for-profit model would have two important benefits. The first concerns resistance. Removing the need to obtain profit through sales volume would make it easier to restrict use of any ensuing antibiotic. Second, *“it would be a very important means of preventing companies from pulling out of antibacterials. In the light of current trends away from antibiotic research, this type of set up would maintain the environment that permits the production of a diversity of antibiotics against a wide range of need.”*

“We need a forum to bring people together to ask what can be done... What is needed are enough people to go at this together... If you could bring people together in a non-confidential way you could widen the net as far as it needed to go. I think this kind of initiative is best done by something like the EU, rather than by any specific government.”

We need *“to develop models for shared risk, shared cost and shared profit.”*

“We need a joint venture where everyone realises each others’ strengths and weaknesses and mutual interests and commitment. Academics are good at ideas but downstream medicine development needs companies.”

“You could say to the companies, we’re prepared to devote a lot of money to this if you’re prepared to give us ideas about how you’d do

something for TB or MRSA, or it could be academics, or it could be jointly. There are various ways to do it to get the ideas up about the targets that are worth going for, and then be prepared to do some risk sharing with them. It really does need Europe and the United States together.”

A joint public private venture *“may be a way of developing alternative payment measures and models.”*

A KICK START

For some, the intervention would only be needed to get the early research kick-started. *“What you need is a little fund whose mission is to find these people and identify the promising research. It’s a scouting role; the money could come from public bodies, some foundations, and maybe a VC (venture capitalist) valuation person. I can’t help thinking that if you get it started it could produce wonderful results. You wouldn’t be wasting research, because you still get the scientific findings. And if the outcomes are really good they will attract other things.”*

“I think we have maybe to come back to academia-Biotech partnerships ... so that people with different parts of the jigsaw can come together to create a useful partnership. Government could offer some sort of financial incentive to that sort of consortia.”

“You don’t necessarily need more than initial seed funding. A PPP would need a VC stakeholder to ... do the commercialization, such as looking for Phase III partners, or others to fund ... You reach a certain critical mass through the VC then it gets taken to next stage. They will look out on the product’s behalf. The public health body is interested in the public health aspect, the scientist the science aspect, and the VC the money. It benefits everyone because of the shared risk. A VC would benefit because it has a diversified portfolio. The foundation would benefit from knowing more about the commercial world and government meets public health needs.”

“Public investment should be preferentially available for new classes otherwise it would be an irresponsible use of public money. Public

money could be made available for IP buy-outs, lead buy-outs. You could have someone - a VC person scouting around for value for money propositions. Investors may get money from a buy-out from social venture capital. You need to get away from end pull of the market. The "public" in the arrangement concerns the definition of what you are prepared to buy. A commercial CRO would be able to help you do the regulation."

END MARKETS

For others, in order to meet medical need and the need to control resistance, government should be involved from start to finish in some sort of formal PPP – funding early research and providing clear articulation of the market through advance purchasing agreements. This involvement would provide an opportunity to consider the idea *"of separating out patent rewards from R&D since the rationale that patent "rent" pays for R&D is not really working to deal with public health needs."* It also tackles resistance. *"I am sure one can create a model that [identifies] the sort of pricing regime and market size based on appropriate use... Most revenues currently come from inappropriate use which operates as a perverse incentive. You need to model according to appropriate use."*

"The advantage ... is that you have much greater control of use of an antibiotic that is developed through a PPP. How much it is used, where it's held. If there is no money in it then there is no push to sell on volume. This is the key point."

"It might be interesting to look at prospect of cash buyouts of private sector IP once a confirmed candidate is available e.g. from SMEs/ Biotechs."

LESSONS FROM EXISTING PPPs

There were strong reservations about the transferability of existing PPP models to antibiotics. The prime concern is that any antibiotic resulting from a PPP would have greater commercial potential in richer markets, making management

of IP and discussions about price much more complicated than existing agreements which are run purely on a not-for-profit basis. This is particularly true given the likely involvement of both SMEs for whom potential sales may be significant, and Big Pharma whose peak sales figures would need to be higher to be of interest. *"A PPP would replenish the pipeline at the incoming end at very small cost to [the company]. [But] if something comes out of it, they will need an organisation which can move out of discovery and into a product. The issues of access and pricing are difficult issues."*

These unanswered questions about the end market are significant. *"The model of existing PPPs, which assumes that industry will pick up clinical responsibilities (PIII and registration) and bring a drug to market once public groups have "pushed" the project far enough along (PI & II), stimulated by the potential commercial returns, does not work for non-commercial drugs as the incentive to PIII investment does not exist. Research "has demonstrated that the PPP type structure can incentivise initial research by reducing some of the costs upfront... However... even by reducing the risks, you haven't made the project commercially interesting enough for commercial enterprises to pick it up downstream because of the really expensive phase III. PPPs haven't yet brought in private funding to match downstream so you remain wholly dependent on public dollars to do it."*

A possible solution to this is bifurcation, with the creation of a not-for-profit foundation for early development stages – which run until up to end of phase II. Any resulting product could then be licensed to commercial companies for sale in industrialised markets while distribution in developing countries could be undertaken on a not-for-profit basis. Prices in developed country markets are likely to be extremely high under this model.

It should not be assumed that a PPP would be capable of meeting developed and developing country needs simultaneously. Developing countries are likely to need pull mechanisms including a commitment to buy large quantities at low price. This may be different from a PPP for industrialised markets which may want to focus on resistance, keeping volume down and prices high.

Section Six: General Conclusions

THE PROBLEM

1. Limits of the existing market structure

The structure of the pharmaceuticals market does not provide the right incentives for sufficient investment in antibiotics to meet rapidly changing medical need. Only two new classes have been discovered in the past thirty years. Of the fourteen antibiotics expected to be launched between 2005–2010 all but one are additions to existing classes.

2. Likely Health Consequences

The likely consequences, already discernible, are increased levels of mortality and morbidity associated with a lack of access to effective antibiotics. The prognosis for five to ten years time, due to drug development times and lack of existing research in the pipeline, is grave. There is only one new class in late stage development.

3. Outline of Unmet Medical Need

There are a range of unmet medical needs in the antibiotic field that will require different solutions:

- Treatments are needed for new infections and emerging resistances in developed countries, particularly in the field of Gram negatives;
- Treatments are needed for community-acquired resistant infections in all markets;
- New medicines are needed for diseases that predominantly occur in developing countries, such as TB, typhoid fever and gonorrhoea. Innovation in developing countries needs to encompass both formulation and presentation of the treatment. And it is vital to simultaneously tackle the issue of misuse of antibiotics.

There is widespread concern about the lack of successful research into Gram negative pathogens and in particular those Gram negatives that are more common in the community and currently picking up resistance to existing antibiotics. The emergence of these resistant bacteria demonstrates how the antibiotic landscape is constantly changing and requires continued and committed research.

4. How the Market Works

A great deal of public money is invested in pharmaceutical R&D. Nevertheless, at the heart of the current model of drug development is a profit-seeking private enterprise. To undertake research and development requires significant investment. Companies have to be able to argue that returns on that investment are competitive. This means of determining how capital is allocated is extremely problematic for antimicrobials which now risk become subject to the same funding difficulties as other neglected disease areas.

Antibiotic Return on Investment

The reasons for relatively poor antibiotic return on investment are varied and inter-related. First, the most commercially promising drugs are those that treat the symptoms of long-term, chronic diseases. Antibiotics used to treat acute illness for a short duration do not make so much money. Second, the consolidation of the pharmaceutical industry has left fewer people doing antimicrobial research in fewer companies. Third, the science of antibiotic discovery is particularly difficult. Fourth, in a highly genericised market, the overall price antibiotics command is low. Fifth, the push to reduce antibiotic use to prevent the spread of resistance is acting as another disincentive. Sixth, the regulatory environment is increasingly risk averse and is particularly onerous for antibiotics. And finally, given that resistance inevitably develops for all antibiotics over time, the lifespan of these drugs is inherently limited.

Could price incentives improve the situation?

Increased prices could provide a financial incentive for antibiotic innovation. To achieve this, reimbursement authorities would need to be persuaded of the value associated with the increased price. This is difficult given that health budgets tend to be highly departmentalised. Even if such calculations were done, price increases are not universally supported because they do not address the financial access barriers posed to developing countries, to people in industrialised countries with insufficient or no prescription drug coverage and increasingly to health insurance systems – State and private – for whom increased medicine prices are becoming unsustainable.

Nor will price increases be an attractive incentive to create antibiotics for use in primary care. While reimbursement authorities may be prepared to accept extremely high, but containable, prices for limited-use medicines in intensive care settings, they are unlikely to do so for community acquired infections, where the health budget implications are much harder to predict.

It may be possible to do more to produce different categories of antibiotics which are priced differently. Those used for general public use could come under one pricing regime, while others used selectively to treat seriously ill patients come under another. For this to be successful, reimbursement agencies would need to accept different needs in different clinical settings and be prepared to act accordingly.

Are SMEs a more effective vehicle than Big Pharma?

SMEs, with their much reduced infrastructure costs and their ability to accept lower profit margins may prove to be a better vehicle for antibiotic development than Big Pharma. However, while SMEs may find it easier to obtain funding to take drug development to the end of phase II, they will encounter the same difficulties as Big Pharma in obtaining funds for Phase III, by far the most costly period of drug development. Providing them with technical and regulatory support to take the drug through later stages of development could make a material difference.

Market Failure

The net result of these financial constraints has made it more difficult to justify investing in antibiotic research. The result is that there are only a handful of new antibiotics in the pipeline. This is a serious market failure, given the clear scientific gap and medical need these drugs need to fill.

5. The Role of Government in Stimulating Antibiotic R&D

Participants agreed that where there is a societal good that is not met by the market, it is entirely appropriate for government to intervene. Given financial constraints on antibiotics, all those interviewed agreed that government should take action to address market failure. At the moment, while there is growing political will to deal with the spread of resistance and to increase surveillance capacities, particularly to tackle MRSA, governments need to do more on antibiotic innovation. The study was not designed in such a way as to permit precise conclusions about the nature of government support for antibiotic innovation. A more detailed review is needed.

Nevertheless the Study did throw up interesting ideas that could help frame such a review. For some, government should play a role within the existing market structures, by investing substantially in early research, by removing barriers to innovation and by redefining what constitutes value for money in antibiotics and consequently paying more for true innovation. Others were in favour of a more concerted, government-convened effort that could amount to some

sort of public private partnership. Within this group some argued that the market failure to produce new antibiotics provides an opportunity to review how to de-link innovation from end-profit for non-commercial medicines.

6. The Scientific Challenges Research Leads

There is no consensus as to whether enough targets for antibiotics are being developed. But whether there are enough targets or not, their subsequent development remains the core issue. The principle impediments to this development remain finance and time. Further research into the problem of latency and the persistence of dormant infections is needed.

The promise of genomics

The science of genomics still offers great potential that past disappointments should not be allowed to overshadow. But for this to yield fruit, investors and companies need to be more realistic about the complexity of the science and how long it will take to yield results.

A Public Library?

A public library of rejected chemical substances could be set up and made widely available to anyone able and willing to develop them. The criteria for eligibility would be some sort of public guarantee of use. A shared chemical library of this kind would help compensate for the fact that existing libraries are tending towards chemicals that bind human receptors. Such chemicals are unlikely to be useful as antibacterials. A linked proposal was to make early scientific discoveries open source.

Diagnostics

One area of scientific research that could make a huge difference in the field of antibiotics is diagnostics. Diagnostics could deliver many significant innovations for antibiotics including:

- a point of care test to differentiate between viral and bacterial infections, thus permitting doctors to know whether to prescribe antibiotics;
- improvements in pre-clinical tests for pharmacology and toxicology to identify safety problems as early as possible;
- help in the identification and validation of biomarkers;
- the development of alternative biological endpoints to complement clinical endpoints.

Finding the exact causative bacteria of an infection is far more difficult to do than is appreciated by most people. Expense, turnaround time and the liability implications of inaccurate test results are all impediments to the uptake of diagnostics in the management of infectious diseases. It was argued that government research bodies, such as National Institutes for Health or the Medical Research Council, could provide substantive inputs to support this work.

Vaccines

There is no vaccine that specifically targets antibiotic-resistant bacteria. Successful research into a vaccine that specifically targets antibiotic-resistant bacteria could prevent the spread of resistant infections, thus reducing antibiotic use, and so avoid future resistance. The development of the meningitis vaccine was described as providing important lessons which might be applicable to support vaccine development in the antibiotic field. Though, there are many differences between the two, government guarantee of the final market was important to the success of the project. The speed with which government has responded to the need for a vaccine for the potential pandemic spread of a human variant of avian flu also sets an encouraging precedent.

7. The Regulatory Environment

The Normative Regulatory Environment: Risk Aversion

Prevailing social norms about what constitutes an acceptable risk-benefit equation dictate how much information is required to demonstrate that medicines are high quality, efficacious and safe. Regulations currently come down firmly on the side of risk aversion. This risk-benefit equation needs to be tested against patient views in all markets. In addition, it is important that regulations are not unfairly blamed for decisions taken by the pharmaceutical industry on commercial grounds.

Removing Barriers to Innovation in the Regulatory Process

Overall, it was argued that the whole clinical trial process could be more efficient, and the question asked as to whether improvements could be made to the particularly rigorous trial requirements for antibiotics. These arise because companies seek to market medicines as widely as possible, trials are required for each indication, and because increased resistance has led to increases in the information requirements for some antibiotics to prove superiority.

It is at Phase III – the most expensive of all the trial phases – that many feel the changes need to be made. There are various possible means of delivering short cuts, including improved diagnostics (see above).

Reducing Patient Numbers

More could be done to reduce the number of patients required for trial which could significantly cut the costs of trials, particularly if better surrogate end points were permitted. The cost of bringing antibiotics to market should be lower than other therapies – scientists have a lot of best practice shared amongst their community. There are short, well defined end points, and trials are relatively short due to the duration of treatment.

Improved Statistical Probability

Phase III trials could also be made more agile by using alternative statistical measures to those currently used. Bayesian statistics in particular were mentioned as an alternative means to calculate probabilities of trial outcomes.

Fast Track Registration and Priority Review

Fast Track registration and priority review procedures to speed up the process of bringing a drug to market are already available

in both Europe and in the US. There are examples of where they have been successfully used for antibiotic innovation. However, providing SMEs with support to use these procedures has the potential to increase their capacity to bring innovation to market. Speeding up the review process by increasing staff in reviewing bodies would help. Fast Track could also help with the specific need for antibiotics in developing countries.

Orphan Drug legislation

Orphan Drug legislation is designed to encourage R&D into diseases for which there are inadequate market incentives due to the small number of patients suffering from the disease. It provides additional incentives to those provided by the market, including extended market exclusivity. Though at first glance it appears that Orphan Drug-type legislation could be effective in providing incentives for some hospital-acquired, restricted use, high priced drugs, the lessons from the Orphan Drug experience are not necessarily transferable to antibiotics. Orphan Drugs by definition treat a small number of patients. Due to a potentially much larger (and much less predictable) patient base, there is a danger that the costs to health budgets of extended market exclusivity would be prohibitively high. In addition, the Orphan Drug model is inappropriate for developing country settings where the greatest needs are for a cheap, simple to use and robust first-line therapies.

Post-Marketing Surveillance

It is not possible to confidently measure risk until the number of people exposed reaches more than 100,000 which exceeds the requirements of Phase III. It would therefore make sense to reduce the number of patients in trials and significantly increase post-marketing surveillance.

However, the benefits of conditional registration are not straightforward particularly in the light of resistance. First, from a commercial perspective, if the trade-off of bringing a drug to market earlier means restricted labelling, the problem of incentive is not solved. Second, health authorities are limited in what they can do in the event of company non-compliance with the requirement to provide more data. Third, for some, surveillance data, as currently presented is more like marketing than scientific findings. To meet this concern, improved surveillance could be achieved through a pan-European project for electronic patient records to monitor pharmacovigilance.

Tax Credits

There are a number of other options that can be used to encourage innovation, but none were strongly advocated in this round of interviews. Although tax credits to incentivise R&D have been effective in the implementation of Orphan drug legislation, it appears that additional pull incentives of a clearly defined market have to be in place for them to work. Thus tax credits alone would be insufficient as incentive.

An Advance Purchase Agreement

Some argued that to meet the dual challenge of resistance (existing and future) and the need for incentives, government and health

insurance schemes should come to agreement with industry about an advance purchasing agreement which makes payment independent of volume. Others stated that the same goals could be met by ensuring that pricing is more determined by clinical effectiveness giving industry and price-setting bodies greater certainty. The development of the meningitis vaccine was described as a success story in which government guarantee of the final market played a critical role. There are also valuable lessons about the pros and cons of advance purchasing of other vaccines, and of growing evidence that the widespread use of vaccines is increasingly linked to a decline in resistance. However, others took the view that the end market is so fragmented that coming to an agreement on an advance purchasing agreement would be too complicated. There may be significant differences between the US and Europe in this regard due to the differences in reimbursement structures.

Transferable Intellectual Property Rights

The proposal under Bioshield II for Wild Card IP provision, whereby companies are allowed to transfer patent rights from a less to a more profitable product, was acknowledged in interviews. However, no-one proposed this as appropriate for the development of new antibiotics.

8. Thinking Outside the Market

Even if a package of incentives were successful in promoting innovation for some new antibiotics, there was unanimous agreement that some medical needs would not be met: new infections and resistances in both developed and developing country settings – particularly in the field of Gram negatives; medicines for community acquired infections in all markets; and existing resistant diseases in developing countries – such as TB, gonorrhoea and typhoid fever. In this instance, interviewees all agreed on the need for some sort of more assertive public intervention or a more formal PPP to facilitate antibiotic innovation. What such intervention might consist of was not clearly defined, but a number of interesting suggestions about how it might work were made.

A fully not-for-profit model would have two important benefits. The first concerns resistance. Removing the need to obtain profit through sales volume gives much greater control of use for any ensuing antibiotic. Second, an agreement of this nature would be a means of preventing companies from pulling out of antibacterials. In the light of current trends away from antibiotic research, this type of set up would maintain an environment which encourages the production of a diversity of antibiotics against a wide range of need.

A Kick Start

For some, government intervention should only be needed to provide an injection of capital to support a scouting fund to identify and buy out promising research. From there, the proposition could become self-financing.

End Markets

For others, in order to meet medical need and the need to control resistance, government should be involved from start to finish in some sort of formal PPP – funding early research

and providing clear articulation of the market through advance purchasing agreements. This would permit a structure that allows innovation to separate out patent rewards from R&D.

Lessons from Existing PPPs

Despite this enthusiasm, there were strong reservations about the transferability of existing PPP models to antibiotics.

The prime concern is that any antibiotic resulting from a PPP would have greater commercial potential in richer markets, making management of IP and discussions about price much more complicated than existing agreements which are run purely on a not-for-profit basis. This is particularly true given the likely involvement of both SMEs for whom potential sales may be significant, and Big Pharma whose peak sales figures would need to be higher to be of interest.

A possible solution to this is bifurcation, with the creation of a not-for-profit foundation for early development stages – which run until up to end of phase II. Any resulting product could then be licensed to commercial companies for sale in industrialised markets while distribution in developing countries could be undertaken on a not-for-profit basis. Prices in developed country markets are likely to be extremely high under this model.

High regard was expressed for the expertise of scientists outside industry, but most interviewees acknowledged that the consolidation of technology and knowledge in the pharmaceutical industry, particularly about what is druggable, meant that many scientists lack expertise on key aspects of translational research.

Existing PPPs have demonstrated that this type of structure is able to incentivise initial research by reducing some of the costs upfront, but it has not solved the question of when and how to make the project independent of public funding.

Commercial expertise is vital for the success of any PPP. In particular, people highlighted the need for a) scouting (along the lines of venture capitalist model) to identify promising research, b) commercial know-how, particularly about how to determine whether a promising lead is druggable, c) expertise in phase III regulation and trials (though it was acknowledged that much of this knowledge is now outsourced and available through CROs).

It should not be assumed that a PPP would be capable of meeting developed and developing country needs simultaneously. Developing countries are likely to need pull mechanisms including a commitment to buy large quantities at low price. This may be different from a PPP for industrialised markets which may want to focus on resistance, keeping volume down and prices high.

Whatever the model for bringing the antibiotic to market, the end product would be entering a market in which there is considerable reluctance to pay for high priced antibiotics. This reluctance may increase in line with pressure for reduced prices of pharmaceutical products more generally. Any model that is premised on high prices would therefore need to factor in overall healthcare budget benefits of effective antibiotic treatments.

SUPPORTING REFERENCES

Infectious Diseases Society of America, Bad Bugs, No Drugs, July 2004

Kaplan, W. & Laing, R. "Priority Medicines for Europe and the World", WHO November 2004

Kettler, H. & Towse, A. "A Review of IP and Non IP Incentives for R&D for Diseases of Poverty": Submission to the CIPIH, 2005

Love, J., Hubbard T., "A New Trade Framework for Global Healthcare R&D", Public Library of Science, February 2, 2004

Nordberg, P., Monnet, D., Cars, O. "Antibacterial Drug Resistance: Options for Concerted Action", WHO, Feb 2005

The Pink Sheet, 15 Dec 2003: R&D Outsource Spending To Rise 14% A Year; CROs Will Gain The Most

Rawlins, M.D. Cutting the Cost of Drug Development, Nature 2004; 3 360-364

Spellburg, B., Powers, J.H., Brass, E.P., Miller, L.G., Edwards, J.E. Jr. "Trends in antimicrobial drug development: Implications for the Future", Clinical Infectious Diseases 2004;38:1279-86

APPENDIX ONE

Interviewees

1. Stewart Adkins
Pharma Analyst
Lehman Bros
2. Dr Bo Arronson
Group Leader, Anti-infectives
EMEA
3. Dr Han de Neeling
National Institute of Public Health and the
Environment,
The Netherlands
4. Dr Jorgen Dirach
Section on Medicines Development,
European Federation of Biotechnology
5. Dr Jeff Edwards
Former Director of Clinical Microbiology,
Infection Therapy Area
Astra Zeneca
6. Dr. Shereen Elfeki
Healthcare Correspondent
The Economist
7. Dr Maria Freire
Executive Director
TB Alliance
8. Mr William Haddad
Chairman and CEO
Biogenics Inc
9. Dr Yusef Hamied
Chairman
Cipla
10. Professor Robert Johnston
Professor of Microbiology and Immunology,
University of North Carolina & Director of the
Carolina Vaccine Institute
11. Kees de Jonchere
Regional Adviser for Health Technology and
Pharmaceuticals
WHO Regional Office for Europe, Copenhagen
12. Dr. Warren Kaplan
School of Public Health
University of Boston
13. Dr. Hannah Kettler
Programme Officer, Policy and Finance
Gates Foundation
14. Jamie Love
Director
Consumer Project on Technology
15. Dr Dominique Monnet
National Center for Antimicrobials & Infection
Control
Statens Serum Institut, Copenhagen, Denmark
16. Dr. Mary Moran
Director Pharmaceutical R&D project
LSE
17. Prof. Malcolm G. P. Page
Head of Biology
Basilea Pharmaceutica Ltd
18. Dr Bernard Pecoul
Executive Director
DNDI (Drugs for Neglected Diseases Initiative)
19. Prof. Sir Michael Rawlins
Chair
National Institute for Clinical Excellence (UK)
20. Dr. Alison Thomas
Director of Global Research, Value Reporting
PWC
21. Prof. John Turnidge
Associate Professor of Medicine and Director of
Microbiology and Infectious Disease
The Women's and Children's Hospital in Adelaide,
Australia
22. Dr. Anthony White
Former Director of Antibacterial Scientific
Communications,
GlaxoSmithKline
23. Mr Andrew Witty
President, Pharmaceuticals Europe
GlaxoSmithKline
24. Ben Yeoh
Pharma Analyst
Williams de Broe

