Chapter 34

The Pharmaceutical Company Approach to Antibiotic Policies

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1. INTRODUCTION

The word "policy" is defined as "prudent conduct, sagacity; course or general plan of action (to be) adopted by government, party or person." In this sense, antibiotic policies range from local hospital or community policies to national treatment guidelines for specific infections, regulatory policy, and regional and global strategies. All have the potential to impact on the pharmaceutical industries' (Pharma) integrated activities of discovering, developing, and marketing antibacterials. This article reviews the relationship between antibacterial policies and the role of Pharma.

For almost 70 years, Pharma has played a major role in discovering, developing, and making available antibacterials for human and veterinary use (Garrod *et al*., 1981). Today, more than in recent decades, there are high demands on Pharma to deliver to patients new, effective antibacterials to replace those agents for which clinical utility is compromised by emerging bacterial resistance. This "crisis," with the daunting prospect that one of the most beneficial discoveries and developments in the history of mankind could become extinct within a mere few human generations, has understandably also prompted a wide range of recommendations, guidelines, and policies with the intent of preserving and protracting the utility of our current antibacterial armamentarium. However, in some cases, these policies themselves are

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reducing the chance of success of Pharma delivering the antibacterial agents for the future.

In order to succeed, Pharma will need to adapt to the new environment, but there is a very real and immediate danger that the extent of change in the environment is presenting significant hurdles that will prevent or delay the discovery and delivery of new agents. A greater understanding of the collective impact of policies on Pharma's ability and willingness to conduct sustainable research and development (R&D) of antibacterials is needed along with a cooperative partnership approach. There is a need for governments, non-governmental organizations (NGOs), policy-makers, regulators, and infectious disease experts to collaborate with Pharma to establish ways to maximize the chance of bringing new antibacterials into clinical use and sustain their utility. Unfortunately, individual Pharma companies continue to exit from antibacterial discovery and development and the pool of major companies is likely to soon be occupied by a handful or less, severely restricting the ability of Pharma to meet the medical needs of infectious diseases, particularly those which require flexibility and responsiveness, such as epidemics and those arising from bioterrorism. Once R&D efforts are terminated it will require substantial new investment, both in monetary and intellectual terms, as well as time to re-initiate effective programmes. Without continued, sustainable, and successful antibacterial R&D, we will certainly be facing the prospect of "antibacterial extinction."

2. THE PAST

There is no doubt that *research-based* Pharma has for many years been instrumental in providing the wide range of clinically important agents which are available today. Garrod *et al*. (1981) described three eras of antimicrobial chemotherapy:

- *alkaloids*: from 1619 and use of cinchona bark to treat malaria
- *synthetic compounds*: from 1909 and the discovery of the arsenical salvarsan by Ehrlich, and including Prontosil/sulfonamides in 1935
- *antibiotics*: from 1929 with the discovery of penicillin.

Pharma has been predominant in discovering or developing antibacterials in the two most recent of these three eras. While not all antibacterials were discovered by Pharma, many of the early members of today's antibacterial classes were brought to clinical use through the development and scale-up activities of Pharma, in some cases through collaboration by a number of companies, notably in the development of penicillin G in the 1940s. The majority

of discoveries and developments that have produced the major classes of antibacterials, as well as the many significant developments within these classes, have been the result of the Pharma industries' innovation and expertise.

It is probable that without the efforts of research-based Pharma and the associated integrated competitive and commercial aspects, many of today's agents would not yet have been discovered, developed, or available to physicians. The now somewhat famous declaration in 1969 by the US Surgeon General, William Stewart, testifying before US Congress that it was time to, "Close the book on infectious diseases," illustrates the degree of success that was perceived to have been achieved at that time.

3. THE PRESENT

3.1. Pharma and the "crisis"

Although there is a sector of the Pharma industry that focuses on the sale of generic versions of agents discovered and developed by the research-based companies, these activities mainly require only manufacturing and distribution expertise. Now, as in the past, it is the research-based companies to which we need to continue to look to for the provision of agents for the future.

The discovery, development, and appropriate use of new agents is a key theme in the major antibacterial strategies and policies to combat resistance which have been reviewed by Carbon *et al*. (2002). Against this background it may be considered surprising or even alarming that the Interscience Conference on Antimicrobial Agents and Chemotherapy for 2003 (ICAAC, 2003) includes a symposium entitled *Why is Big Pharma Getting Out of Anti-Infective Drug Discovery?* A review of abstracts on *new* antibacterial agents or targets/methods presented at ICAAC 2002 indicates some 47 companies involved in this field including 10 of the "top 12" companies as determined by sales (Table 1).

Of the total, 32 companies presented data from established classes (β-lactams/inhibitors, lipopeptides/glycopeptides, fluoroquinolones, oxazolidines, protein synthesis inhibitors) and 8 of these companies were from the top 12 companies by sales. Twenty-one companies presented data on targets or methods, thirteen exclusively, and seven on novel agents or immunomodulators (Table 1). This analysis represents only a snapshot of those companies presenting at ICAAC and not the total discovery programmes currently being undertaken, some on areas not yet disclosed, others since terminated.

Despite the wide range of presentations by Pharma at ICAAC 2002, there has undoubtedly been a consolidation in antibacterial R&D in the large Pharma companies, and a dearth of novel agents emerging from the pipelines.

Table 1. Companies involved in the development of new antibacterial agents presented at ICAAC 2002

Type of agent	Companies involved
Carbapenems	Meiji Seika Kaisha Ltd, Sankyo Company Ltd
Cephalosporins	LG Chem Investment Ltd, Takeda Chemical Industries Ltd, Basilea Pharmaceutica AG, *Shiongi & Co Ltd, Johnson & Johnson*
Oxapenems	Amura Ltd
Lipo- and glycopeptides	Cubist Pharmaceuticals Inc, *Eli Lilly & Co, Wyeth Research*, Biosearch Italia SpA, *Aventis*, Theravance Inc
Fluoroquinolones	Wakanuga Pharmaceutical Co Ltd, *Abbott Laboratories*, Wockhardt Research Centre, *Bayer AG*, Dong Wha Pharm Co Ltd
Oxazolidines	Ranbaxy Research Laboratories, AstraZeneca, Dong-A Pharm, ImaGene, Morphochem AG, *Johnson & Johnson*, Versicor Inc, *Pharmacia Corporation*, Dr Reddy's Laboratories Ltd
Protein synthesis inhibitors (macrolides and ketolides)	*Aventis, Johnson & Johnson*, Enanta Pharmaceuticals Inc, Versicor Inc, Novartis Pharmaceuticals Corporation, British Biotech Pharmaceuticals Ltd, Optimer Pharmaceuticals Inc, *Bayer AG*
Other new agents and immunomodulators	*F Hoffman La Roche AG* (diaminopyrimidine), Meiji Seika Kaisha Ltd (caprazamycin), *Bayer AG* (dipeptide), Versicor (LpxC inhibitor), Genesoft (hetero-aromatic polyamides), Xechem Inc (rapamycin), Biocryst Pharmaceuticals Inc (purine nucleoside phosphorylase inhibitor)
Targets and discovery methods	AstraZeneca, *Aventis*, Quorex Pharmaceuticals, Daiichi Pharmaceutical Co Ltd, Proteomic Systems Inc, Arrow Therapeutics, Genome Therapeutics Corporation, GPC Biotech AG, *Eli Lilly & Co*, British Biotech Pharmaceuticals Ltd, NewBiotics Inc, PanTherix Ltd, Schering-Plough Research Institute, *Wyeth Research, GlaxoSmithKline Pharmaceuticals*, Influx Inc, Genelabs Technologies Inc, *Bayer AG*, ImaGene, Pantheco A/S, *Pharmacia Corporation*

Note: Names in italics are major pharmaceutical companies that feature in the top 12 (by sales).

Increasing discovery activity in smaller companies may offset this, although the capabilities of smaller companies to develop antibacterials to market may be limited in the face of increasing development hurdles. The future model of discovery and development may well have to rely on collaborations and cooperations between small/discovery and large development/supply Pharma.

Mergers and acquisitions have resulted in the key players becoming significantly fewer and each withdrawal from antibacterial development has an

increasingly significant impact on the potential for new antibacterials becoming available. The top 12 leaders in the field of antibacterials in terms of sales in 2002 (GlaxoSmithKline Pharmaceuticals, Pfizer/Pharmacia, Bayer AG, Abbott Laboratories, Aventis, Johnson & Johnson, Roche-Chugai, Bristol-Myers Squibb, Wyeth Research, Shionogi Seiyoku, Eli Lilly & Co, and Merck & Co) have evolved from some 20 to 30 companies with antibacterial R&D heritages. Some are the result of none or few amalgamations while others are many-fold.

Of the top 12 companies, less than half are believed to be currently active in antibacterial R&D. Within the remaining companies the discovery effort has been directed towards either defined niche disease areas, or large "block-buster" commercial areas, with a consequent reduction in diversity across the industry. Individual specializations within Pharma, such as was the case when companies almost exclusively worked on penicillins (Beecham Research Laboratories), cephalosporins (Glaxo), or quinolones (Bayer AG), for example, are becoming less as the companies look to satisfy commercially attractive target product profiles from whichever molecular classes that are available through their R&D efforts or in-licensing. The emphasis on development of line extensions of existing molecules has also increased as a means to improve patient benefits such as convenience and efficacy and importantly for Pharma, to maintain development and commercial activity to offset patent loss and bridge the gap to the introduction of new agents. Critically, of the companies which have exited or severely reduced their antibacterial R&D (e.g., Aventis, Bristol-Myers Squibb, Eli Lilly & Co, Roche-Chugai, and Wyeth Research) (IDSA, 2003), these decisions have been taken relatively recently at a time when the need for new effective antibacterials is arguably greater, but also at a time when policies and regulations for the development and use of antibacterials have proliferated.

The crucial issue will be the ability of companies, big or small, alone or in collaboration, to bring novel agents to the market and whether the agents being discovered and developed today will satisfy both the medical and the commercial needs to provide a sustainable future for antibacterial chemotherapy. Continued investment and commitment of big or small Pharma into research for new antibacterials to meet current and future clinical needs is crucial and yet is at a crisis and being impacted by antibacterial policies which are increasingly being developed and implemented.

The Infectious Disease Society of America (IDSA) newsletter, March 12, entitled *The Future of Antimicrobial Drug Availability: An Impending Crisis* (IDSA, 2003), highlights the current issues facing the development of antimicrobial drugs. Infectious diseases are the second leading cause of death and the leading cause of disability-adjusted life years worldwide. Antibacterials are key tools in treating many globally important infectious diseases, including meningitis, pneumonia, diarrhoeal illness, skin and bone infections, tuberculosis, sexually transmitted infections (gonorrhoea, syphilis, and chlamydia),

HIV/AIDS-related bacterial infection, and diseases that may be spread as a result of bioterrorist acts. Withdrawal from antibacterial research will have a major impact on global health. A letter to the journal of the American Society for Microbiology (Appelbaum, 2003) states that, "A crisis has developed and we are doing nothing about it," highlighting that Pharma companies are reducing or closing their antibacterial research and that pipelines are, "practically empty." Appelbaum suggests that, unlike drugs for long-term treatments, there is a lack of funding for research into antibacterials, one of the reasons for this being the overly stringent approval criteria imposed by the Federal Drug Agency (FDA), making it practically impossible or prohibitively expensive to bring new antibacterials to market (Appelbaum, 2003).

For those who have worked in the antibacterial field from the hey-day of discoveries in the 1960s and 1970s it is very apparent that the number of new chemical agents being progressed to man and subsequently marketed is much reduced. IDSA reported that of 89 new medicines reaching the US market in 2002 none was an antibacterial, with only 7 new antibacterials being approved since 1998 (IDSA, 2003). A review of company reports for the 11 major Pharma companies listed only 4 new antibacterials in the drug pipeline out of 290 agents listed (1.38%) (IDSA, 2003) and that on average the time to develop new antibacterials was 7–10 years from discovery to first approval. Although Pharma has continued to explore ways to increase efficiencies and decrease development times, these have largely remained stable due to the increased numbers of patients required for new drug applications (NDAs), as well as increased complexity and costs in meeting regulatory approval requirements (Kaitin and DiMasi, 2000). An important consideration for Pharma companies involved in R&D and commercialization of therapies for a range of disease areas, is that other therapeutic areas are increasingly more profitable than antibacterials. Today, there are fewer large companies specializing in antibacterials as a main R&D area. Investment decisions are made across and between therapeutic areas and Pharma has an obligation to maintain shareholder value and commercial viability or else no new drugs would become available in any therapy area.

The reasons for the "crisis" in antibacterial R&D, manifested by fewer new agents or classes reaching clinical use, are complex and multifactorial but undoubtedly the impact of the changing environment of regulations, guidelines, and policies on the development and use of antibacterials is an important contributory factor.

3.2. Antibacterial resistance and policies

Stated simply, antibacterials are developed and used to overcome bacterial infection. The progressive discovery and introduction of new classes and

agents extended the range of bacteria and associated infections that could be successfully treated. Antibacterial resistance, which has emerged from the beginning of antibacterial chemotherapy, has provided a key medical reason for the development of new agents, along with the wish to improve efficacy, safety and tolerability, and dosing convenience. Anti-infectives are unique (with the exception of some increasing evidence in oncology) in that the target of their action can change and provide the rationale, medical need, and commercial incentive for the development of new agents. The need for new agents or classes to combat antibacterial resistance is arguably greater today than it has been for some decades.

Concerns about emerging resistance, increasing loss of utility of existing antibacterials and associated negative impacts on health have given rise to a wide range of strategies (strategic plans, action plans), policies (rules and directives), and guidelines or guidance. Some are advisory and others mandatory but all constitute broad policy with respect to the development and use of antibacterials. The sources of policy activities range from global NGOs, such as the World Health Organization (WHO), regionally based bodies such as the European Union (EU) and European Medicines Evaluation Agency (EMEA), country-based public health and regulatory bodies such as the Centres for Disease Control (CDC), and FDA, and physician associations (IDSA), to the local, and institutional level within countries. A comprehensive summary of the more influential recommendations for the control of antimicrobial resistance has been prepared by Carbon *et al*. (2002). Some 17 separate national recommendations, from eight countries are listed (Australia, Belgium, Canada [2], France [2], Finland, Sweden [2], United Kingdom [3], United States [5]). In addition there are five international recommendations: two from the EU (Copenhagen recommendations, 1998; Community Strategy against Antimicrobial Resistance, 2001), one from ICAAC 1999 (Summit on Antimicrobial Resistance), one from Toronto (Toronto Declaration, 2000), and one from the WHO Global Strategy for Containment of Antimicrobial Resistance (2001). All these recommendations date from 1994 to 2001 with the majority being published between 1998 and 2000. Undoubtedly, there are more or updated recommendations in the pipeline and continuing activities of bodies addressing the topic, such as the USA CDC Task Force (IDSA, 2003; Shlaes and Ryan, 2003).

Common themes, which emerge from the range of recommendations related to antibacterials and antibacterial resistance, are the need for:

- surveillance of resistance and antibacterial usage
- optimizing antibiotic use (reduce inappropriate use), guidelines, and policies
- education of professionals and patients into judicious/prudent use
- prevention through infection control, interventions, immunization
- focused development of new agents, diagnostics, and strategies

- regulatory/label guidance, prescribing, and advert restriction
- audit of evaluation of intervention and compliance.

The objectives of most strategies and policies are to better control antibacterial use with the intent of reducing or preventing antibacterial resistance. This, accompanied by parallel activities to monitor and understand resistance (such as its consequences and relationship to antibiotic use), improve infection control, and development of new agents (antibacterials and vaccines) and therapeutic approaches, is hoped to provide a sustainable solution in combating bacterial infection.

Carbon *et al*. (2002) state that these recommendations rightly focus on controlling resistance in the community through surveillance of resistance and usage, and education of prescribers and the public in judicious antibiotic use. Nevertheless, the authors point to the need for more research to fill substantial knowledge gaps, notably the reversibility or containment of resistance with the optimization of antibiotic usage has yet to be definitely established (Carbon *et al*., 2002; Davey *et al*., 2003). It is suggested by Carbon *et al*. (2002) that for now, antimicrobial management programmes should focus on ensuring the most appropriate use of antimicrobials rather than simply on limiting choices. Interventions must also be audited for effectiveness/cost (Christiansen *et al*., 2002). It is also suggested that the programmes in the recommendations can not succeed if they do not imply the active contribution of health professionals, politicians, consumers, and Pharma, and that the creation of optimal conditions for this type of cooperation is of critical importance (Carbon *et al*., 2002; Chahwakilian, 2000). The key role of Pharma in these strategies is to deliver new antibacterials, although the cumulative impact of the parallel recommendations may present significant barriers to achieving this aim (Figure 1).

3.2.1. Surveillance of resistance and usage

Surveillance programmes of bacterial susceptibility have become commonplace in the field of antibacterials over the last decade and feature in most recommendations and policies relating to combating resistance. The principles of surveillance, key studies, data, and issues have been extensively reviewed (Bax *et al*., 2001; Felmingham *et al*., 2002; Hunter and Reeves, 2002). Good quality surveillance methodology and interpretation are essential to the understanding of resistance emergence and its control. The main functions for surveillance were described by Felmingham *et al*. (2002) as:

- quantification of resistance: resistance prevalence/distribution/changes over time
- guidance for antibiotic use: individual patient level/guidelines/policies

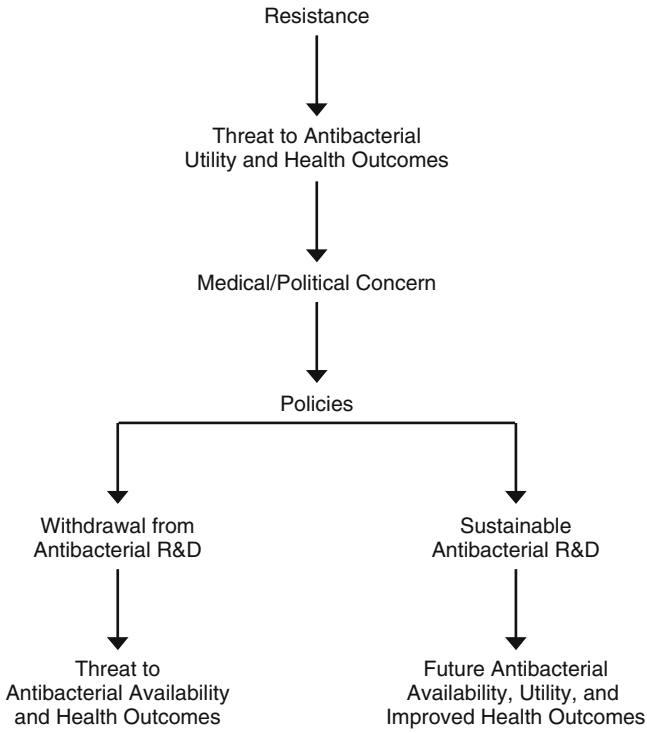

Figure 1. Two potential consequences of policies and strategies to combat resistance.

- research/education: epidemiology of resistance/link with usage
- industry: R&D/licensing/marketing/post-marketing
- resistance control: design of strategies/impact of strategies/interventions.

Pharma is both a generator and user of surveillance. Additionally, all the functions for surveillance described by Felmingham *et al*. (2002) have the potential to impact Pharma's development strategies and potential success in delivering new antibacterials. The relationship between resistance, antibiotic usage patterns, and clinical outcomes is an important factor in determining policies for antibacterial use. Scientifically robust methodologies and interpretations are critical but have not yet been fully defined or attained for many surveillance studies (Bax *et al*., 2001).

Pharma itself has been actively involved in the initiation and support of a number of key surveillance studies over many years (Felmingham *et al*., 2002).

These studies are mostly aligned with the companies' discovery and marketing interests but nevertheless have provided good quality data in many cases where data were lacking and even pre-date the recent calls in strategy and policy documents for antibacterial surveillance. Indeed, global studies, such as the Alexander Project (Felmingham *et al*., 2002), initiated in 1992 and funded by SmithKlineBeecham (now GlaxoSmithKline) pioneered the standardization and quality control of methodology across countries and laboratories in the surveillance of bacterial resistance in community-acquired lower respiratory tract infection and provided a model for a number of subsequent global and national studies.

Pharma involvement and funding in surveillance may be a continuing necessary and desirable role. Pharma need data from which to establish and drive the need for R&D activities into new antibacterials. Surveillance data are also needed for product labelling, such as the resistance prevalences required, for example, by EMEA. Susceptibility data from surveillance are important to support product differentiation and benefits in the market place, and may also be required as part of a Phase IV regulatory commitment for a new agent. Academia and policy-makers also need such data to assess the antibacterial environment and the appropriate policy and practice interventions and outcomes. All parties need good quality, scientifically valid data. However, there may be differences in needs regarding the scope of studies, such as the organisms that are included, the agents tested, or the reporting of data (minimum inhibitory concentrations vs susceptible/intermediate/resistance), but the demand for quality and accuracy of interpretation should be equal.

A key issue is the source and sustainability of funding of surveillance, along with ownership, interpretation, and dissemination of data. Global or regional, longitudinal surveillance studies are extremely expensive and resource intensive. Individual Pharma companies have initiated and solely sponsored studies to support the development and marketing of new agents (Bax *et al*., 2001; Felmingham *et al*., 2002; Hunter and Reeves, 2002). This creates a situation where at a particular time a number of Pharma companies may compete for collecting centres for key isolates and be funding a number of laboratories to screen similar isolates and agents while at other times or for other pathogens or agents, there may be little Pharma support, or data available from any source. Surveillance funded by government, societies, or other non-Pharma sources may not meet Pharma's specific needs. Conversely, Pharma's studies may not meet broader needs (Bax *et al*., 2001; Lewis, 2002), or be perceived as "distorted" source of data because they are funded by Pharma (Lewis, 2002). Pharma support for large single-sponsored surveillance studies is dependent on successful product registrations and marketing. Similarly, Pharma support for broad regional and national studies, of value to strategists and policy-makers in these areas will become limited in an environment of reduced investment and commercial success. Collaborative surveillance

between and within Pharma and academia or regulators may become increasingly necessary but is difficult to implement in terms of mutually acceptable objectives, scope, methods, timelines, funding agreement, management, and publication/presentation rights. Bax *et al*. (2001) stated that consortium funding will be necessary for large schemes to be successful, and that there is no "ideal" surveillance system.

New approaches to the funding, conduct, and availability of surveillance data while recognizing individual Pharma confidentiality and commercial interests, include the purchasing of surveillance data from commercial surveillance companies or entering into collaborative surveillance studies with specific protocols. Sources of purchased data, such as from Focus Technologies (formerly MRL/TSN) (Bax *et al*., 2001; Hunter and Reeves, 2002), may provide solutions to many requirements although the extent, quality, and utility of the data is dependent on the database and may not be as well defined or specific for a purpose as a pre-defined protocol. Examples of collaborative predefined protocols are the British Society for Antimicrobial Chemotherapy (BSAC) surveillance projects for respiratory tract pathogens (Reynolds and BSAC Extended Working Party on Respiratory Resistance Surveillance, 2001) and bacteraemia pathogens in which a number of Pharma sponsors support a core protocol and panel of antibacterials, along with the ability to have research agents tested under confidentiality. The results from the core protocol, which has been developed by experts in academia, specialist testing laboratories, and Pharma are made available via the website to the BSAC membership (www.bsacsurv.org). This approach, combining support from a number of companies, with the wide and timely dissemination of core data resolves some of the issues and conflicts relating to quality, interpretation, and dissemination associated with single-company studies and also is hoped to increase sustainability. The current utility of this programme is, however, restricted due to the data and methods being specific to the United Kingdom.

In conjunction with the generation and use of susceptibility surveillance data, there is need for a clear understanding of the limitations, validity, and consequences of studies to correlate antibacterial usage with resistance. The relationship between antibacterial usage and resistance is complex, and while there is a clear association between use and resistance, cause and effect has not been substantially defined (Carbon *et al*., 2002; Davey *et al*., 2003). There are a number of confounding variables that are important to consider in the interpretation of simple cause and effect (Davey *et al*., 2003). Reversibility or containment of resistance with optimization (or reduction) of antibacterial usage has yet to be definitely established (Carbon *et al*., 2002). Consequently, policies designed to curtail or prevent antibacterial resistance based on reduction or change in antibacterial use need to be based on sound science and importantly, the objective of maintaining or improving patient outcomes. Bax *et al*.

(2001) concluded that for surveillance:

1. decisions need to be made regarding the critical populations to be monitored for both local and national comparisons of resistance rates, that is, what level of resistance warrants intervention, and what should be the nature of the intervention;
2. quantitative data are more valuable than qualitative data and all testing must be shown to yield results that are capable of valid comparison;
3. molecular techniques should be used to define strains and detect mechanisms of resistance (see Poupard, Chapter 23);
4. there is a place for both narrow focus and broader surveillance studies: both require funding, but broader studies, including a wide range of organisms and compounds, require consortium funding.

There is a need for the interested parties such as academia, policy-makers, regulators, and Pharma to consider mutually beneficial surveillance programmes, with agreed methodologies and interpretations persuant to their purpose. This approach may not only provide efficiencies in utility, support, and sustainability but also a better understanding of relationship between antibacterial use and resistance and the role and impact of policies and interventions.

3.3. Policies, guidelines, and education on antibacterial use

In addition to the key influential recommendations described by Carbon *et al*. (2002) there are many other national and local guidelines, guidances, policies, and educational campaigns which impact antibacterial use. Most such policies either describe the need for implementation of "judicious" or "prudent" use of antibacterials, or use terms such as "misuse" and "overuse" as causes of resistance and imply that a reduction in antibacterial prescribing *per se* will have a beneficial and sustainable effect on resistance. There is a recognition that while prescribing guidelines and other prescribing support systems should help control bacterial resistance in the community, their actual effect on resistance patterns is largely unknown (Finch and Low, 2002) and the reversibility or containment of resistance with the optimization of antibiotic usage has yet to be definitely established (Carbon *et al*., 2002; Davey *et al*., 2003).

Davey *et al*. (2003) described the control of antibiotic prescribing as a crucial part of any strategy to limit the development of resistance as advocated by the UK House of Lords recommendations and the Copenhagen recommendations (Carbon *et al*., 2002). These authors recognized the difficulty in proving that antibiotic policies help to resolve a problem of resistance that has already developed and also recognized the greater difficulty in proving that

policies prevent the development of resistance. Most policies (and guidelines) are concerned with which antibiotic is prescribed and Davey *et al*. (2003) state that it is more likely that development of resistance will be contained by policies which also try to limit unnecessary prescribing of antibiotics (i.e., prescribing for non-bacterial or self-limiting illness).

The general advantages of an antibiotic policy are described by Davey *et al*. (2003) as:

- promotion of awareness of benefits, risks, and cost of prescribing
- facilitation of educational and training programmes
- reduction of aggressive marketing by Pharma
- encouragement of rational choice between drugs based on analysis of pharmacology, clinical effectiveness, safety, and cost;

and specifically to antimicrobials as:

- the promotion of education on local pathogen epidemiology and susceptibility along with awareness of infection control.

The general benefits are described as:

- improved efficacy of prescribing (sensitivity and specificity)
- improved clinical outcome
- reduced medical liability;

and specifically to antimicrobials as:

- limited emergence and spread of resistance.

Davey *et al*. (2003) suggest that antibacterial policies can definitely improve the quality of prescribing and may be used to limit cost and that limiting superinfections and antibiotic resistance should be viewed as additional benefit (and probably not a realistic primary aim). Similarly, Ball *et al*. (2002) stated that when prescribing is necessary, quality prescribing may not only combat resistance and optimize patient outcomes but also provide cost benefits. In a review of the impact of guidelines in the management of community-acquired pneumonia, several studies were identified which showed that an increase in the proportion of patients who receive prompt, appropriate therapy was associated with improvements in outcome measurements such as mortality and length of hospital stay (Nathwani *et al*., 2001).

Gould undertook a review of the role of antibiotic policies in the control of antibiotic resistance, noting that the pragmatic and essential approach to the control of antibiotic resistance is to control antibiotic use (Gould, 1999).

He also noted that policies can be efficacious in reducing costs and levels of antibiotic use, but the subject of debate is whether antibiotic control measures can reduce current levels of resistance rather than just halting it. There are examples where control of antibiotic use has reduced the incidence of outbreak and resistant organisms in hospitals and similar examples where reduction of prescribing in the community has led to a degree of control of resistance. There are a number of confounding factors which make it difficult to attribute cause and effect entirely to reduction in antibiotic prescribing (Davey *et al*., 2003; Gould, 1999). Mathematical modelling seeks to take these factors into account and, while also casting doubts on whether reduction alone will prevent or reduce resistance (Austin *et al*., 1999; Gould, 1999), may help with future understanding of measures which contribute to or reduce antibacterial resistance, and as such should be encouraged. Use of this approach to define policies has been limited (if used at all) (Davey *et al*., 2003). Nevertheless, policy decisions should be supported by evidence, and not just by concerns about future development of resistance or the desire to reduce costs (Davey *et al*., 2003).

Importantly, appropriate use of antibacterials needs a clear definition. It is recognized that recommendations and guidelines should emphasize that the role of antibacterials is for treating bacterial infection, when known or suspected (Ball *et al*., 2002; Davey *et al*., 2003). Use of antibacterials outside of this scenario is unnecessary, contributes to overuse and is an avoidable risk factor in the development of resistance (Ball *et al*., 2002; Davey *et al*., 2003). However, when use of antibacterials is warranted (necessary) to treat bacterial infection, such use may also be inappropriate or suboptimal in terms of choice of antibacterial, dose, or duration. For example, Schlemmer (2001) concluded that antibiotic misuse does have an impact on promoting antibiotic resistance, and that antibacterial choice, dosage, dosing regimen, or duration of therapy must also, therefore, be considered. Carbon *et al*. (2002) suggested that, for now, antimicrobial management programmes should focus on ensuring the most appropriate use of antimicrobials rather than simply on limiting use or choices. A Consensus Group (Ball *et al*., 2002) has recently identified principles for appropriate prescribing of antibacterials in lower respiratory tract infection with which to underlay prescribing and guideline formulation. These principles include:

- identification of bacterial infection by optimized diagnosis
- severity assessment where relevant
- recognition and incorporation of ambient resistance data
- targeting bacterial eradication (or maximal reduction in bacterial load)
- use of pharmacodynamic (PD) indices to optimize choice and dosage
- objective assessment of true (overall) costs of resistance and related treatment failure.

Guidelines, policies, and educational campaigns should seek to better define, support, and implement appropriate use based on principles such as those from the Consensus Group (Ball *et al*., 2002). "Prudent" use or reduction in use alone will not adequately define or ensure optimum or appropriate use of antibacterials. The definition and implementation of appropriate prescribing based on evidence-based optimization of quality antibacterial use (right drug/dose/duration based on PD indices and local resistance patterns), rather than reduction in quantity alone may contribute towards the aim of slowing or preventing the emergence of antibacterial resistance, and also offer associated cost and efficiency benefits. Importantly, this approach may also maintain an environment that supports the use of new effective antibacterials and a commercial rationale for investment and development by Pharma. An ill-defined environment, focusing on the need to reduce quantity with little differentiation between optimal and suboptimal agents is not conducive to the development and marketing of agents with improved activity and efficacy benefits.

3.4. Discovery, development, and commercialization in the face of policies

Increasing development costs and hurdles and shrinking market sizes, means that Pharma has to get more value out of the R&D investment by improving productivity, reducing development timelines, reducing risk, and increasing the value of agents progressed to market. In the case of antibacterials, the situation is compounded by increasingly demanding regulatory policies affecting the activities required to secure product registration, the product label and clinical use (Shlaes and Ryan, 2003). The extent and success of antibacterial research has declined (IDSA, 2003) and is partly a reflection of its relatively low commercial attractiveness compared to other therapeutic areas. The relative return on investment (ROI) or net present value (NPV) of antibacterials is a reflection of the market size and chance of success in capturing a commercially acceptable part of that market. This important "market share" will be a reflection of the properties and utility of the agents along with the success of marketing activities. Differentiation of comparative benefits, such as efficacy against resistant organisms, broader spectrum of pathogens for a given indication, superior efficacy over commonly used treatments, improved dosage regimens and compliance, or better safety characteristics are important features in marketing an antibacterial and in the acceptance and uptake by policy-makers and in the demonstration of cost–benefits to formularies. Policies or guidelines which decrease the ability of Pharma to demonstrate these benefits, reduce the chance of gaining differentiated label indications (such as the inclusion of resistant organisms), or restrict usage to

limited indications (such as only to resistant organisms) will negatively impact NPVs and ROIs for new agents. Development of an antibacterial agent for restricted use only may not be a commercially attractive proposition for Pharma companies with interests in other therapeutic areas.

In order for Pharma to succeed and maintain investment, hurdles in productivity in discovery and development need to be overcome and the key issue of ROI based on product benefits and use needs to be addressed.

3.4.1. Antibacterial discovery and genomics

Although policies themselves do not directly impact upon the process of discovery of new antibacterials, they do have a cumulative negative impact on the chance of success of developing and marketing new differentiated antibacterials and consequently, the willingness of companies to initiate or continue investing in antibacterial discovery research. The urgent need for new classes of antibacterials has, however, increased the pressure in Pharma to maximize efficiencies in identifying new molecular targets for antibacterials and compounds active against those targets. Genomics and high-throughput screening (HTS) offer important potential advances in this area.

On 25 April 1953 Francis Crick and James D. Watson published their paper "Molecular structure of nucleic acids" in *Nature* (Watson and Crick, 1953), describing the double helix structure of DNA. This signalled the launch of the modern era of molecular biology and provided the foundation of our understanding of molecular medicine, transforming much of scientific research including how we approach the discovery of new drugs. On 15 April 2003, nearly 50 years after the publication in *Nature*, Carl B. Feldbaum of the Biotechnology Industry Organization (BIO) announced the "finished" version of the human genome sequence and the completion of the Human Genome Project providing an accurate map of the 3.1 billion units of DNA. At the same time, it was reported that the genome of the newly identified SARS (Severe Acute Respiratory Syndrome) virus had been sequenced in only 6 days. The *Bacillus anthracis*, Ames strain used in postal terrorist attacks in the United States in 2002 was reported as sequenced on 1 May 2003.

The role of genomics in antimicrobial discovery should be considered against the background of Pharma's efforts over many years in fine-tuning the existing classes of antibacterials to improve their spectra, efficacy, and safety through semisynthetic and wholly synthetic chemistry approaches. Linezolid, an oxazolidinone, represented the first novel compound class introduced to the market in more than 25 years (Diekema and Jones, 2000). Traditional chemical modification to produce new members of existing classes has resulted in significant improvements in β-lactams, macrolides, and fluoroquinolones

(e.g., Rasmussen and Projan, 2003), but has been a relatively slow and labour-intensive process with limited additional success in recent years. A team of bench chemists in the 1970s might produce up to 30 novel compounds each per annum for biological screening against a panel of target organisms, resulting in a total, perhaps of hundreds of compounds being screened. For example, methicillin, discovered in 1960 had a Beecham Research number of BRL 1241, and was followed by many valuable semisynthetic penicillins over the next decade, notably ampicillin (in 1961), carbenicillin (1967), and amoxicillin, designated BRL 2333 (1972), indicating the extent of synthesis and screening of this highly successful semisynthetic range of compounds, at approximately 100 per year. Unfortunately, this approach of chemical modification based on knowledge of structure–activity relationships combined with improvements in throughputs of screening has failed to increase the number and diversity of antibacterials in recent times.

Mills (2003) describes genomics-related technologies as they are currently applied to the discovery of small molecule antibacterial therapies. With respect to microbial genomics, the DNA sequence of *Haemophilus influenzae* was published in 1995 (the first free-living whole-organism sequence), followed by *Mycoplasma genitalium* and many other sequenced complete bacterial genomes, of which 79 are publicly available, including those of more than 40 human pathogens.

The process of antibacterial discovery through genomics revolves around the "minimum gene set for cellular life hypothesis" (Koonin, 2000; Mills, 2003) and a number of defined stages in the process.

1. Inventory of essential genes:
   (a) genome-scale transposon mutagenesis to identify all non-essential genes (inferring essential genes);
   (b) expression of anti-sense RNA to probe suspected essential genes, and knocking out conserved genes of unknown function to identify novel "broad-spectrum" essential genes.
2. Identification of target genes:
   (a) select target gene either as narrow- or broad-spectrum by specific conservation profile based on comparative genomic analysis;
   (b) prove essential for *in vitro* growth, for example, by gene knockout in relevant bacteria;
   (c) clone and sequence gene and optimally express protein product;
   (d) purify and develop assay, and screen and identify target inhibitors "hits";
   (e) characterize hits in terms of potency, mechanism of action, spectrum, and selectivity.

For broad-spectrum targets a key issue is to study isozymes from several genetically diverse bacterial species along with further screening against a panel of microbes for cellular activity, particularly to address the potential role of intake cell membrane barriers or efflux mechanisms (MDRs) on antibacterial activity. Lead compounds can be further optimized in terms of potency, spectrum, and selectivity through studies on the mode of action (MOA). Optimization of pharmacokinetic (PK) and PD properties through distribution, metabolism, and PK (DMPK) studies and drug delivery/formulation are increasingly important areas in the development process. In particular, knowledge of the role of PK/PD in relation to appropriate dosing and the potential for resistance development is evolving and is being used increasingly by Pharma.

The proof of principle of this genomics-driven, target-based approach, starting with a conserved gene and leading to antimicrobial compound is the discovery of BB-3497, a peptide deformylase inhibitor with Gram-positive and Gram-negative activity. Optimization by HTS is exemplified by methionyl tRNA synthetase. A target identified through genomics and genetics and to which whole-cell screening of target-specific inhibitors has been undertaken is LpxC, a metallo-enzyme essential for growth of Gram-negative bacteria. High-density DNA microarrays is a technology undergoing validation which has the potential to generate a vast amount of functional information on coordinated gene expression under various growth conditions.

There are a number of new antibacterials currently in late-stage development, although all of these are from existing established classes (e.g., penem, fluoroquinolone, glycopeptide, lipopeptide, glycylcycline) (Rasmussen and Projan, 2003). It is hoped that use of genomics to identify novel targets with biological and clinical relevance and HTS to increase the chance of "hits" may result, in time, in a range of novel antibacterials for development (Mills, 2003; Rasmussen and Projan, 2003). Many, if not all, of the bacterial targets have now been identified, but HTS has yet to deliver the range of novel antibacterial compounds that hit these targets. Encouragingly, the most advanced HTS plants now have the capacity to screen 300,000 compounds per day. Worryingly, there are increasing hurdles in the development and commercialization of antibacterial agents that might adversely impact the willingness of companies to initiate or continue investing in antibacterial discovery research.

3.5. Antibacterial development, labelling, and benefits

New antibacterials are unlikely to be recommended as first-line clinical agents in policies designed to control antibacterial use unless they offer benefits, often assessed in relation to cost over existing branded or generic

agents. Efficacy against organisms resistant to other antibacterial choices is a potential benefit but if it is the sole indication it may be of limited commercial attractiveness. There are a number of significant hurdles in being able to demonstrate and use differential benefits. These relate to governmental/regulatory policy with respect to clinical development, product labelling, and promotion.

Shlaes and Ryan (2003) reviewed the strategic and regulatory considerations in the clinical development of anti-infectives. A new and evolving set of challenges exists for Pharma in the clinical development of antibacterials with a number of requirements from existing or proposed regulatory guidelines posing significant hurdles and complexity. The key points of concern to Pharma are listed below.

1. Removal of *in vitro* activity from product label (FDA)—limits potential for description of agents' full spectrum of activity (such as against rare or bioterrorism pathogens), differentiation and promotion.
2. Post-marketing surveillance of resistance and label updates (as required (FDA and national EU agencies))—presents "unlevel playing field" with established/older products.
3. Requirement for *in vitro* percentage susceptibility of organisms from EU countries (Committee for Proprietary Medicinal Products [CPMP])—requires product-specific broad surveillance (organisms and geography).
4. Powering of clinical trials to 10% non-inferiority powered at 90% level (FDA, CPMP)—substantially increased patient numbers and cost.
5. Placebo-controlled superiority trials requested for acute otitis media and acute exacerbations of chronic bronchitis (FDA, CPMP)—increased patient numbers and increased risk of not achieving relevant outcomes.
6. Paediatric rule (FDA); the requirement to progress paediatric indications/registration—increased or earlier resource/cost for paediatric studies.
7. Specific indications, for example, pharyngitis, otitis media, rather than upper respiratory tract infection (FDA, CPMP)—larger number of Phase III randomized controlled comparator studies required to achieve a broad label.
8. Bacteriological study populations and endpoints requirements (FDA, CPMP)—bacteriological endpoints required for breakpoints, labelling, and differentiation.
9. National comparators and resistance in EU (CPMP)—additional studies needed to address national comparators.

The regulatory guidelines are increasingly focusing on the need for demonstrations of non-inferior clinical efficacy in randomized controlled trials in the specific indication. In the United States, inclusion in the product label of only those organisms isolated from the indication under study and for which clinical

cure was achieved is proposed, irrespective of the *in vitro* activity spectrum. Label indications are a key point to control antibiotic use (Schlemmer, 2001) and any information given to the prescriber that is able to help select for proper indications is potentially an important tool for good antimicrobial practice (Schlemmer, 2001). However, Schlemmer (2001) also states that there is a critical need for trials to select for those patient populations who really need antibiotics, or to look for new endpoints able to differentiate between drugs, rather than only demonstrating equivalence. This approach may ensure that clinical evidence supports the claim for beneficial activity against a particular organism in a particular indication, or population, but inevitably will restrict the breadth of label.

The commercial implications of limited labels based on proof of superior benefits (and not just equivalence), compared with broader labelling based on equivalence will be critical to Pharma. The value of studying new endpoints for differentiation will also be dependent on acceptance of the endpoints by regulators, and their incorporation into product labelling, enabling promotion and communication. The differential benefits would also need to translate into guidelines and formulary inclusion. It has been argued by Monnet and Sorensen (2001), that antimicrobials that represent real innovations are readily accepted by hospital prescribers and naturally gain market shares. The hurdle is in being able to demonstrate the innovative benefits to the satisfaction of the regulators and decision-makers, and in there being sufficient commercial return from use in a narrow-defined patient group.

A particular issue is that there will be significant hurdles in the ability of Pharma to demonstrate clinical efficacy against emerging resistant organisms, which may only rarely be isolated in clinical trials. PK/PD data which allow predictions of bacteriological efficacy to be made and tested, for example, in *in vivo* infection models of simulated human PK, or in small PD studies in patients, have been proposed by a number of bodies, including the EU CPMP (EMEA). However, the use of such data has yet to be fully accepted and adopted by the FDA as a surrogate for clinical efficacy and breakpoint determination. PK/PD data are of particular interest when trying to define the best dosage and dosing regimens for new compounds. As the bacteriological endpoint correctly defines the outcome in an infectious process it would serve to assess the PK/PD relationship of a drug (Schlemmer, 2001). Using PK/PD data to predict bacterial eradication or clinical outcome should be considered as the only way to select for optimal therapeutic regimens regarding antibiotic choice and dosing regimen as well as determining the optimal therapy duration (Ball *et al*., 2002; Schlemmer, 2001). A greater role of predictive PK/PD data and modelling under certain circumstances and for specific target populations, has been proposed by CPMP (EMEA) and is supported in general by Pharma.

Global Pharma need to conduct clinical development programmes that satisfy the highest requirements of both FDA and EMEA. In Europe, there is a

need to include comparative agents approved and relevant to individual EU countries, or for which a consensus justification can be argued, for technical approval (EMEA). Phase III clinical trials are designed primarily to meet the requirements of the regulators. However, these traditional comparative non-inferiority trials fail to provide important evidence of potential benefits over existing therapies. With clinical success for antibacterials in the 85% or more level, demonstrations of superiority require vast patient populations. Pharma rely on other data to indicate superiority and benefit, ranging from potency (minimum inhibitory concentrations, etc.), per cent susceptibility based on breakpoint, *in vitro* and *in vivo* models, PK/PD, and defined clinical studies to demonstrate bacteriological and health-outcome benefits. Much of the clinical work undertaken to secure regulatory approval fails to best demonstrate the role and clinical benefits of new agents (Bax *et al*., 1999) and yet is often used as the evidence base for reimbursement, guidelines, and policies. There has also been a proposal to update and harmonize antibacterial product labels between European countries, particularly for "old" antibiotics and their datasheets (summary of product characteristics) at the time of generic introductions because lack of relevant product information promotes inappropriate use (European Conference on Antibiotic Use in Europe, 15–17 November, 2001; Schlemmer, 2001). The burden of cost to provide new data to demonstrate the benefits of marketed and new agents would lie with the Pharma R&D companies. Failure to produce data to support current claims could result in removal of differentiation from established branded products, while provision of data may strengthen the labels of generic products.

Bax *et al*. at the Whitley Park Symposium in 1999 reviewed the limitations of the current clinical evaluation process and stated that the lack of development in how to define precisely both drug value and appropriate use will seriously hamper the drug industry's ability to develop important new medicines discovered by new technologies (Bax *et al*., 1999). The authors suggested that what is needed is further and much more rapid development of conventional means of drug evaluation, such as the clinical trial, as well as visionary use of new methods in epidemiology, and new use of electronic data merged in a way that identifies drug effects on both a population and individual basis.

4. THE FUTURE

4.1. Collaboration, collaboration, collaboration

The role of R&D-based Pharma is to discover, develop, and commercialize antibacterials. There is a danger that the wide range of policies which have been introduced under the auspices of "combating resistance" will themselves

hamper Pharma's ability to deliver a key strategy, if not the most important weapon in the battle against bacterial infection and resistance, the introduction of novel antibacterials. Policies and improvements in the quality of antibacterial prescribing have an important role to play, as do diagnostics, vaccines, infection control, and other interventions. Pharma is clearly an important partner along with government, NGOs, regulators, infectious diseases experts, practioners, and patients in the battle against bacterial infection. The "conflicts of interest between the prescriber, the regulator, and the profit maker" was the subject of a supplement to *Clinical Microbiology and Infection*. The editor (Gould, 2001a), recognized that the calls for restrained use of antibacterials to combat and control resistance counters the natural instincts of doctors to do the best for their patients and of Pharma, which of necessity, needs to profit to exist and continue.

It is, however, unfortunate that Pharma can be regarded first as "profit makers" and can even be excluded from contributing to debates on the subject of antibacterial use (European Conference on Antibiotic Use in Europe, 15–17 November 2001). There needs to be a distinction between companies which are solely suppliers of generic products and those who have the objective, dedication, and expertise to discover and introduce new antibacterials. These are undoubtedly profit makers, being subject to commercial and shareholder expectations, but perhaps should be considered foremost as "providers" with respect to new antibacterial solutions. Gould describes an international partnership of medical societies and industry, in association with regulators as a model for the future in the battle against antibacterial resistance (Gould, 2001b). Schlemmer (2001) highlighted that while antibacterial policies were the keystone in promotion of good antimicrobial practice, more accurate and relevant information on antibiotics is urgently needed and that it is the responsibility of Pharma and regulators to move together towards an improvement in antibiotic evaluation. The objective would be to give prescribers more critical product information and to help the experts create better guidelines.

WHO included Pharma via the International Federation of Pharmaceutical Manufacturers Association (IFPMA) in consultation on their *Containment Strategy and Model Prescribing Guidelines* (www.who.int/emc/amr.html) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) have represented Pharma in EU and EMEA discussions and consultations on clinical trial guidelines and labelling. In the United States a multiagency task force of FDA, CDC and the National Institute of Health (NIH) issued a document entitled *Public Health Action Plan to Combat Antimicrobial Resistance* in 2001 with a priority to create an interagency antimicrobial resistance product development working group coordinated by the FDA, US Department of Agriculture (USDA), and CDC (Shlaes and

Ryan, 2003). A second priority was to, "Investigate and act upon potential approaches for stimulating and speeding the entire antimicrobial resistance product development process, from drug discovery through licensing," including exploring the economics of the situation and incentives. While Monnet and Sorensen (2001) argue that much investment from Pharma is into marketing and not R&D and that the so-called "R&D Scare Card" is not justified, it is clear that Pharma companies are increasingly taking the commercial decision not to invest in R&D for antibacterials, but in other areas. According to Shlaes and Ryan, incentives for increasing Pharma R&D into priority infectious diseases include the need for more information on the market and disease areas (based on market identification, disease-specific bioinformatic systems, development of surrogate endpoints), more predictability (based on market assessment, international regulatory harmonization, and reinforcement of intellectual property rights), and more cost–risk sharing (market creation, patent extension, orphan drug legislation) (Shlaes and Ryan, 2003).

A number of bodies, such as WHO, IDSA, and EU task forces have begun processes to assess the situation and identify some areas of action. These include:

- summarizing the value of antibacterials
- identifying the status of clinically relevant resistance and priority pathogens
- evaluating the state of antibacterial research/regulatory submissions/industry involvement and outlook
- maintaining databases of funding agencies, their research interests, new opportunities for funding
- documenting the vulnerabilities related to the manufacture of antibacterials/shortages/negative impacts on public health: gap analysis
- undertaking the identification, prioritization, and tracking of global public health needs (a global agenda)
- reviewing/documenting government activities to foster development of new antibacterials
- reviewing recommendations for "incentivizing"
- modifying regulatory approval processes such as priority review, fast track, waiver of user fees, orphan drug status, modified/smaller clinical trials, and/or reduced number of efficacy studies per indication (and use of surrogates such as PK/PD)
- harmonizing clinical trial methodologies and implementing coordinated action by regulatory agencies in registration of new products
- increasing education and training opportunities.

Research-based Pharma needs to be included as a partner in these collaborative initiatives in order to help shape the future in a way which will be conducive to

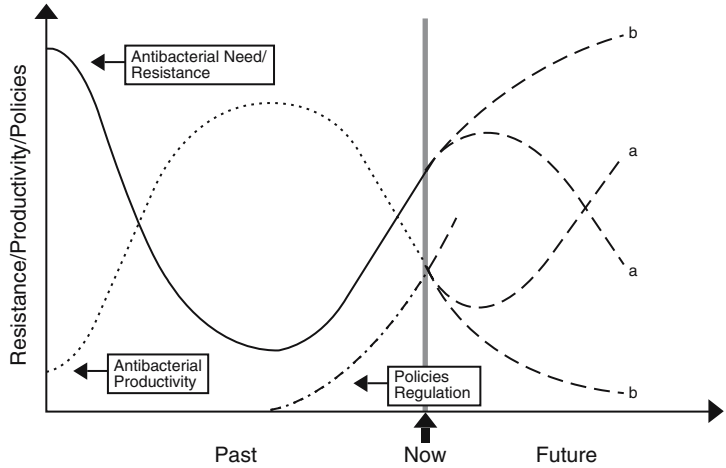

Figure 2. From the past to the future: Hypothetical potential scenarios evolving from the relationship between antibacterial need/resistance, antibacterial productivity and policy. (a) Sustainable balance of antibacterial productivity, resistance, and regulation/policy; oscillations may decrease over time with better understanding of the relationships and balanced management. (b) Crisis of imbalance of increased policy/regulation, decreased incentives and antibacterial productivity and increasing/uncontrolled resistance.

continued investment into R&D for new antibacterials while improving their use and sustainability. This will require a full consideration of the contributing factors, actions, and impacts in order to find a way to maintain a critical balance (Figure 2). A new model may need to be defined which explores alternative roles of small companies, government, and NGO bodies along with big Pharma in the conduct and funding of antibacterial discovery, development, and distribution.

5. CONCLUSIONS

Policies are important and necessary in controlling antibacterial use in an attempt to preserve the utility of existing and future antibacterials. They should aim to minimize unnecessary and inappropriate use, as avoidable risk factors in the development of resistance, while maintaining or improving patient outcomes. The effect of antibacterial policies on the containment or reduction of resistance is largely unknown and should focus not on quantity of prescribing alone but on quality to ensure appropriate prescribing in terms of antibacterial choice, dosage, dosing regimen, or duration. Policies that relate to

antibacterial use have the potential to reduce the antibacterial market size and commercial attractiveness relative to other therapeutic areas. Policies that relate to development activities and labelling have the potential to increase development costs, restrict use, and limit the ability to differentiate benefits. Collectively policies are negatively impacting big Pharma's willingness to continue investment in this field. The combined and cumulative effects of the various policy items related to surveillance, use, clinical trial guidelines, product labelling, and promotion require a broad, collaborative, and global view of the impact on Pharma R&D. Collaboration is required to identify agreed and mutually acceptable ways to streamline development, implement appropriate prescribing, demonstrate and promote product benefits, and maintain financial incentives.

Antibacterial discovery, development, and use are related within a dynamic environment that includes bacteria, their resistances, and policies. As with any dynamic environment, change will alter the balance (Figure 3). Policies are contributing to a change and a negative impact on the potential and willingness of Pharma to develop new antibacterials. While change may require adaptation for survival and success, careful consideration and collaboration is needed by all parties to help to ensure that insurmountable hurdles are not created leading to the inability of Pharma to survive and succeed in antibacterial R&D. Failure of Pharma to deliver new antibacterials would lead to "antibacterial extinction."

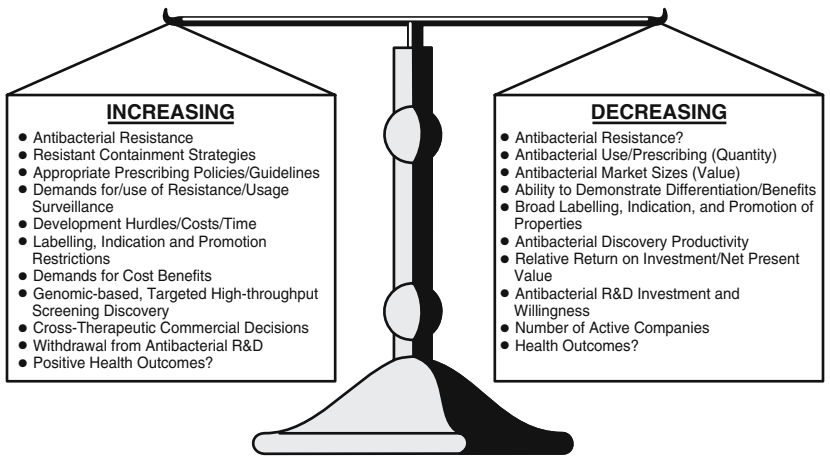

Figure 3. A question of balance: increasing and decreasing factors in the environment of antibacterial resistance, usage, discovery, and development.

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