How to evaluate and predict the ecologic impact of antibiotics: the pharmaceutical industry view from research and development

R. Bax

Chief Scientific Officer, Biosyn, Inc., Philadelphia, PA, USA

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INTRODUCTION

Bacteria represent the great success story of life's pathway. They occupy a wider domain of environments and span a broader range of biochemistries than any other group. They are adaptable, indestructible and astoundingly diverse [1].

The pharmaceutical industry is going through enormous changes. During the 1960s and 1970s the industry emerged globally, new products were introduced and profits soared. For example, in 1980 the market for third- and fourth-generation cephalosporins was increasing at nearly 30% per year, an increase that was not sustainable. New breakthroughs in products for other therapies such as ibuprofen for arthritis (Boots), propranalol for hypertension (ICI), cimetidine for peptic ulcer (SmithKline Beecham), and fluoxitine for depression (Lilly) led to enormous increases in the retail market for nonhospital products and fueled the so-called 'me-too developments' or, to be more politically correct, 'fast followers'. The global antibiotic market in 1970 was approximately 50:50 oral:injectable, which was partly skewed towards injectables that were high priced and largely used in Japan and Italy. This changed because of significant price restrictions in Japan and Italy and an increase in the community market. By value the ratio is now 70 : 30 oral: injectable. The global antibiotic market is now worth over £20 billion. Of the oral market, over 70% is for the treatment, in most cases empiric, of respiratory tract infection. The highest use is in children with infections such as acute otitis media and for the elderly with acute exacerbations of chronic bronchitis or even for acute bronchitis type syndromes.

Pharmaceutical company trends in research and development (R&D) include a focus on big products, a shorter time in development and shorter times to peak sales, leading to increased profitability [2]. The new mega-mergers will exaggerate these trends. When the rationale for the Glaxo SmithKline merger was announced in January 2000 [3] the theme was 'to improve the two groups' ability to generate sustainable long-term growth and enhance share holder value in an increasing competitive market'. Value was seen as global leadership and R&D strength that would lead directly to shorter time in development and shorter time to peak market share. No mention was made of either company's workers except to say there would be synergies and cost savings; also no mention was made of the sustainable ecology or societal value of the corporation.

Against this background, it is clear that if a large pharmaceutical company wishes to develop a new antibiotic, the ideal product would be, by definition, a broad spectrum of oral agents for use in respiratory tract infections. This is the business reality, where there is an absolute requirement to optimize the return on investment. Most large pharmaceutical companies invest approximately 20% of their yearly expenditure on R &D. Big products make big profits for the pharmaceutical companies. In other words, they make much more money on one product with a peak yearly turnover of £1 billion than on five products with turnovers of £20 million each.

R&D costs for a new product range from £500 million to £1 billion. When I left SmithKline Beecham in 1999 the yearly R&D budget was £850 million and one new drug application was lodged each year. In other words, that product cost SmithKline Beecham £850 million to bring to market.

These large costs must be regained. It is estimated that in order to recoup such costs the product must have a turnover at peak of over £500 million. Oral products with current sales of over £500 million include co-amoxyclav, ciprofloxacin, clarithromycin and azithromycin, with moxifloxacin and gatifloxacin not far behind. Of the injectables, only ceftriaxone has sales of around £500 million, with imipenem not far behind. If you were the CEO of a large pharmaceutical company, what product type would you develop if you had the choice?

Corresponding author and reprint requests: R. Bax, Chief Scientific Officer, Biosyn, Inc., Philadelphia, PA 19006, USA
Tel.: +1 215 914 0900
Fax: +1 215 914 0914
E-mail: rbax@biosyn-inc.com

It is often stated that antibiotics are used for a shorter period when compared with other therapeutics because of the development of resistance. It is interesting to note that in spite of the the significant development of bacteria resistant to ciprofloxacin the market for that product has been increasing every year since its launch. Overall, the use of antibiotics in most markets is static but the value of the market is increasing by approximately 3–5% yearly because pharmaceutical companies are successful in changing prescribing trends from low cost generic products to cost branded products. Notably in some countries, such as Sweden, both the overall use and the market for antibiotics has reduced significantly because of a highly successful public health campaign.

The FDA, on 19 September 2000, proposed placing special warnings on virtually all antibiotic prescribing information, reminding doctors to prescribe only when truly necessary and explaining when that would be. The label would also include tips for doctors to use in counseling patients about proper antibiotic use. The FDA will consider mandating the new labeling soon. It remains to be seen what impact this measure will have on overall antibiotic prescribing.

As part of the push and pull policy, the FDA is also considering a drug exclusivity program to encourage investment in the development of antibiotics targeted at resistant bacteria. This 'patent protection' initiative proposed by the FDA would need legislation and may entice large and small companies to develop new and novel narrow spectrum antibiotics that may arise from the new research technologies, such as bacterial genomics, high through-put screens and combinatorial chemistry. The FDA is granting priority to companies developing such compounds, which include early access and accelerated approval. Vaccines that prevent bacterial infections are being highlighted. In fact, because of the potential problem of suboptimal supplies of flu vaccine this winter, the FDA is 'promoting' the use of pneumococcal vaccine to high-risk groups!

The key to appropriate antibiotic use is to be able to quantify the effects of antibiotic use on clinical benefit and microbiological end-points, including the eradication of bacteria and/or the development and spread of sensitive or resistant strains. What is needed is the right antibiotic at the right time, prescribed for the right patient, at the right dose and for the right duration. Rapid increase in the preciseness of clinical trials, and the development of new assessment tools such as mathematical modeling and database analysis where usage of antibiotics is linked prospectively to bacterial surveillance and clinical outcomes are needed. Rapid R&D of novel antibiotic classes as well as co-ordination and co-operation is needed [4].

The effects of bacterial resistance on other biological organisms, including humans, are extremely broad. Individual perceptions of the concept of 'environment' range from effects on individual cells to global considerations. Concepts that address specific topics within this broad scope include bacterial surveillance, biodiversity, population density and evolutionary theory, biomarkers and clinical research in all its aspects including phase I–II proof-of-concept studies, controlled clinical trials and epidemology studies. Mathematical modeling may be particularly useful because each level of organizational complexity introduces new properties and compensatory processes that are not evident from the study of a lower level of organization by itself. Ecologic risk assessment is another useful tool that has been defined as the process that evaluates the likelihood that adverse ecologic effects may occur or are occuring as a result of exposure to one or more stressors (US environmental protection agency framework for ecologic risk assessment EPA1630/R-92/001/Risk Assessment Forms 1992). The broad scope for ecologic risk assessment for antibiotics is represented in Figure 1.

Adverse ecologic effects may be evaluated at levels of biological organization ranging from bacteria to individuals to ecosystems through to global effects. Although not reflected in the diagram, there is also a continuum of spatial and temporal scales, from short-term localized effects of a relatively small use of antibiotics to long-term global effects that may result in, for example, a large increase in the overall exposure to antibiotics. The ecologic risk assessment process as defined by the US Protection Agency should go through three phases: problem formulation, analysis and risk formulation (Table 1).

The problem formulation phase involves evaluating the potential stressors, ecologic effects and ecosystems at risk, selecting appropriate end-points and developing hypotheses that will be the focus of the assessment. Data on ecologic effects, stressor–response relationships, and exposure to stressors, e.g. antibiotic use and/or rates of development of resistance, are evaluated in the analysis phase. In risk characterization, exposure and effects information is integrated, and all of the evidence is brought together to reach a final conclusion about the likelihood and consequences of effects. Effective risk characterizations acknowledge uncertainties and assumptions, and separate scientific conclusions from policy judgments (Table 2).

My pessimistic forecasts for the next 5 years are that, in conditions where the spread of both sensitive and resistant bacteria will increase, the overall burden of antibiotic use, i.e. in humans, animals and plants, will not be significantly reduced; the pharmaceutical industry will continue to provide persuasive information on antibiotic use; most of the information will endorse use of patented products; the antibiotic market will continue to increase in line with average pharmaceutical products; the introduction of novel antibiotics will increase significantly; most will be narrow spectrum; some will be useful and some will not.

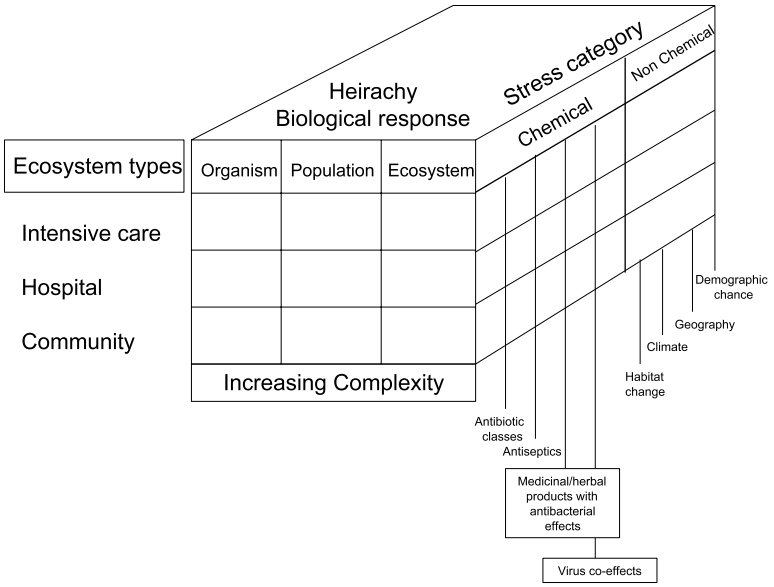

Figure 1 Risk assessment of ecologic impact

Table 1 Ecological risk assessment problem formulation

Problem formulation
Evaluate stressors
Select appropriate endpoints
Develop hypotheses
Analysis
Exposure and ecologic effects
Process modeling
Risk characterization
Exposure and effects information considered
Final conclusion about the likelihood and consequences of effects
• Must acknowledge uncertainties and assumptions
• Separate scientific conclusions from policy judgement[a]

[a]From Fed Regist. 1996; 61: 47552–47631.

Table 2 Ecologic risk assumptions

Effects of antibiotic use on:
• Development of resistance
• Resistance on clinical outcome
• Resistance on bacteriologic outcome
Effects of resistance on:
• Individuals
• Groups
• Populations
• Ecosystems

These activities are complex and need to be achieved by a multitude of interested parties. The role of governments, regulators, nongovernmental organizations as well as the public needs further debate and action. All of us need to be involved. Questions such as the following need to be debated. Is increasing bacterial resistance leading to decreased patient outcomes and/or increased cost? Is there clear and transparent analysis? Are the data available and sent to those who need to know? Is there a mutually agreed action plan? As regards companies, who will provide the checks and balances? Will companies carefully consider and study the ecologic effects?

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