Antibiotics business: A glimpse

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Early history of medicine is largely supported by the secondary metabolites from microorganisms. Before the introduction of antibiotics, between 1940s and 1950s, patients with bacteraemia suffered from low survival chances, and mortality from tuberculosis was well above 50%. The emergence and spread of antibiotic resistant pathogens has increased substantially over the past two decades. At the same time, the development of new antibiotics has decreased alarmingly, because pharmaceutical companies are pulling out of antibiotic research. Reasons include, the changes in regulations of elaborate drug trials, clinical preference for narrow spectrum compounds, prolonged post marketing surveillance, hence the cost of development.

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Introduction

Discovery of antibiotics is one of the greatest events in the history of medicine which has a profound effect on human life, thus in society as a whole. By definition antibiotics are low molecular weight natural products (secondary metabolites) of microorganisms and are active against other microorganisms. Since late 1930’s there was a dramatic development of infection management with the use of antimicrobial drugs. The impact of this discovery has been felt in different ways. There is no fear of devastating disease like plague or surgery is no longer a desperate gamble with human life. The death due to meningitis, tuberculosis, malaria, leprosy, septicaemia once a common incident, are now in rarity. In 1994, the US Office of Technology Assessment (OTA) reported that in USA alone, death of 19,000 patients each year were due to hospital acquired bacterial infections, treatable until recently with antibiotics. Antibiotics are also used for several other purposes, which include hypocholesterolema, immunosuppression, cancer, bioherbicide, bioinsecticide, coccidiostat and as animal growth promotion. About twelve thousand antibiotics are known today and structurally they are very small molecules like cycloserine (102 daltons) and bacilysin (270 daltons) to polypeptide nisin which contains 34 amino acid residues. Approximately, 55% of antibiotics were produced by the genus Streptomyces which is within the filamentous bacterial group (Actinomycetes), 11% from other actinomycetes, 12% from nonfilamentous bacteria and 22% from filamentous fungi.

Research for drug discovery takes about 10-15 years for a new chemical entity to become a drug, which costs about $ 800 million (for a single drug). Report of bioactive products from microbes maintained its amazing pace: 200-300 per year up to late 1970’s, increased to 500 per year by 1997. In 1996, the world market for antibacterials amounted to over $ 23 billion, involving some 300 natural, semisynthetic or synthetic products. The US antimicrobial market in 1995 included cephalosporins (45%), penicillins (15%), quinolones (11%), tetracyclines (6%) and macrolides (5%) as major products. Major share of European antibiotic market is largely covered by Italy and France and is about 10% of their national drug market.

Currently, the antibiotic era is threatened by the emergence of three adverse circumstances namely, high levels of antibiotic resistance of important pathogens, an uneven supply of novel classes of antibiotics and a dramatic reduction in discovery and development of anti-infective agents. Thus, it necessitates a predictive scenario for designing and
selection of a novel antibiotic through resistant organism.

**Antibiotic Targets**

Antibiotic targets include DNA replication (actinomycin, bleomycin and griseofulvin), transcription (rifamycin), translation by 70-S ribosomes (chloramphenicol, tetracycline, lincomycin, erythromycin and streptomycin), transcription by 80-S ribosomes (cyclohexamidine), transcription by 70- and 80-S ribosomes (puromycin and fusidic acid), cell wall synthesis (cycloserine, bacitracin, penicillin, cephalosporin and vancomycin) and cell membranes (surface affecting polymyxin and amphotericin, channel forming ionophore, gramicidin and mobile carrier ionophore monensin).

Experts feel that scientists should target to develop narrow spectrum antibiotics limited to certain diseases with improved efficacy, which may limit the profit margin of any organisation. Several companies are less concerned for the bacterial diseases due to their small market for new drugs. According to an OTA report, drug effectiveness against methicillin-resistant *Staphylococcus aureus* (MRSA) currently shares a market value of US $ 60 million a year, well below the US $100 million benchmark to decide whether or not to invest in research of a particular area. Also a new drug takes 5 to 15 years to find their way through the clinical trials necessary to demonstrate their efficacy, stability and safety.

**Business Aspects**

Majority of infectious diseases are caused by bacteria and fungi, which affect millions of people worldwide. In the United States, the total drug market is $20 billion. The development of antibiotic resistance, due to its indiscriminate use in last 60 years necessitates the development of new strains and antibiotics (Table 1). Over 1000 new secondary metabolites have been characterized from actinomycetes alone since 1990. *Streptomyces hygroscopicus* produces almost 200 and *S. griseus* over 40 different antibiotics. Conconcerted and systematic programmes to discover and to develop new antimicrobials have enabled us to a considerable extent for the battle against resistance factor. In 1998, the Pharmaceutical Research and Manufacturers of America (PhRMA, Washington DC) reported that 27 antibiotics, 12 antifungals and 14 vaccines were in pipe line.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Short list of recently developed antimicrobial compounds</th>
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<td>Compound</td>
<td>Target</td>
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<tr>
<td>Oxazolidones</td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Streptogramins</td>
<td>Protein synthesis</td>
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<tr>
<td>Boxazomycin</td>
<td>Protein synthesis</td>
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<tr>
<td>Ketolides</td>
<td>Protein synthesis</td>
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<td>LY 333328</td>
<td>Cell wall synthesis</td>
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<tr>
<td>New β lactams</td>
<td>Cell wall synthesis</td>
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<tr>
<td>2-Pyridone</td>
<td>DNA replication</td>
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<tr>
<td>New fluoroquinolones</td>
<td>DNA replication</td>
</tr>
<tr>
<td>Glycyclines</td>
<td>Protein synthesis</td>
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<tr>
<td>Inter-based inhibitors</td>
<td>Protein synthesis</td>
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The antibacterials represent the largest (about 60%) anti-infective segments of the world market. They account for 3 to 25% of all prescriptions and between 6 to 21% of the total drug market of a country and up to 50% of the total drug budget of a hospital. The report released by Kalorama Information, suggests that the worldwide market for antibacterial drug will grow almost $30 billion by 2006. The US market of antibacterial was >$8 billion that included cephalosporins ($3.6 billion), penicillins ($1.2 billion), fluoroquinolones ($0.9 billion), tetracyclines ($0.5 billion) and macrolides ($0.4 billion).

Fungal infections are very common and have doubled between 1980s and 1990s and the bloodstream infections has increased five-fold with an observed mortality of 55%. The world sale of antifungal products is ~$3 billion. Approximately 90% of the fungal infections to man are caused by the species of *Aspergillus*, *Candida*, *Cladosporium*, *Epidermophyton*, *Microsporum* and *Trichophyton*. Antifungal agents now constitute to cover 15-16% of the total activity in the infective area and is expanding at a rate of 20% per annum. In the antifungal market, Pfizer, Johnson and Johnson, Merck and Novartis are the major players. To enhance biological activity, the antibiotics are modified chemically and are called semisynthetics. That includes about 160 antibiotics and derivatives such as β-lactam peptide antibiotics, macrolide polyketides and others. The world market for β-lactam antibiotic is now estimated to be US $15 billion (Tables 2 & 3).

Since 1949, the United States is the major manufacturer of penicillin that amounts to ~83 tonnes.
of sodium penicillin G. In 1982, penicillin production was recorded as >12,000 tonnes and Europe served as the major manufacturing sector. The total production of penicillin in 1995 was ~3300 tonnes, which was five times more than in 1960’s. Currently China is the major player in penicillin G manufacture and accounts for approximately one third of its global production.

Simultaneously, increase in penicillin productivity and high (>90%) recovery rate led to significant cost reduction despite increase in the labour, energy and raw material costs. The price for bulk penicillin G was ~$300/kg in 1953 and came down to ~$35/kg in 1980. In late 1990’s, bulk penicillin price was between $10 and $20/kg and bulk marketed price for 6-APA have been estimated to range from $35 to $40/kg. The price of penicillin G had crashed to $5.8/billion unit (1 billion unit = 635g) from $10.5/billion unit that prevailed in April 2003.

The current antibiotic market is dominated by cephalosporins with an approximate market share of 23%. All clinically important semisynthetic derivatives of cephalosporins are manufactured from 7-aminodeacetoxycephalosporanic acid (7-ADCA) or 7-aminocephalosporanic acid (7-ACA). Some oral products (cephalexin, cephadroxil and cefradine) are obtained from the intermediate 7-ADCA. Whereas cefazolin, ceftriaxone, cefotaxime, cefixime are derived from 7-ACA.

A single semisynthetic cephalosporin, ceftriaxone has a market of $1 billion.

Another group of β-lactam antibiotics is carbapenems. As far as structure goes, the carbapenems differ from penicillins and cephalosporins in that their lactam ring moieties do not contain a sulphur group within the ring. A large number of carbapenems have been discovered. Among them, thienamycin produced by S. cattleya is medically and industrially most important now. But one disadvantage of this antibiotic is that it decomposes in dilute aqueous solution and the decomposition accelerates as its concentration is increased. A more stable and potent derivative, N-formimidoylthienamycin was developed and marketed as imipenem. The molecule has high resistance to bacterial β-lactamases. Imipenem is highly successful antibiotic and its world market,
which had grown to <$500 million by 1995, is among the top ten marketed β lactam antibiotics.

Between 1930s and 1940s, four new classes of antibiotics were approved, each with novel antibacterial targets: sulfonamide, β lactams, aminoglycosides and chloramphenicol. Six new classes were added to the list (tetracycline, macrolides, glycopeptides, rifamycins, quinolones and trimethoprim) between 1950 and 1960. Between 1970s and 1990s no novel class had been licensed and all the new drugs were derivatives of existing classes. In 2000, two new classes of antibiotics were approved for the treatment of diseases caused by Gram positive bacteria; the oxazolidinones (linezolid) and cyclic lipopeptides (daptomycin). In 2004, there were few antibacterial agents in the pipeline.

**Business Challenges**

Nowadays, large pharmaceutical companies are not much involved in antibiotic drug discovery because of unfavourable returns. Hence the Infectious Disease Society of America suggested to extend the life of drug patents as an incentive to industry. The key metric used to prioritize investments in industry is the risk adjusted net present value (NPVR): return in dollars after adjustment for investment and lost income, usually expressed as the number of millions of dollars. A pharmaceutical company with a promising product enters $500 million market to capture 10% of it ($50 million). With advertising and distribution costs, patent-attorney fees and initial cost totaling to 50% of the amount that yield to $25 million over the life of the antibiotic However, it is highlighted incisively that there are three other liabilities in terms of cost, risk and time. Also with experimental cost of animal studies and in vitro studies one can assign a dollar value to set back that might be encountered at each of the three testing phases–toxicity experiments in animals, the first studies in humans and the pivotal clinical trials (Table 6). In addition, there are also opportunity costs, in the form of the loss of money earmarked for the project that could have been invested during the time required for drug development. Each of these expenditures must be subtracted from the estimated $250 million return to obtain the NPVR of the investment. Wyeth Research has estimated that antibiotics have an NPVR of 100, but the oncologic drugs have an NPVR of 300, neurologic drugs an NPVR of 720, and musculoskeletal drugs NPVR of 1150.

Approval time is an important factor that too quantify in terms of costs, is the length of time required to obtain drug approval by regulatory bodies. FDA data shows that the average duration of clinical testing (Phase I-III) is approximately six years, and an additional two years are required for regulatory review (approval phase, time for FDA review and sponsor response time). The situation in Europe is not significantly different.

Despite all such constraints some pharmaceutical companies are trying to develop new antimicrobial compounds. R&D units of pharmaceutical industries are trying to isolate new organisms with new antibiotics and are also trying to modify the molecular characteristics of existing antibiotics to increase their potential with reduced side effects and to overcome the resistance.

Erythromycin, the macrolide antibiotic, is used as an alternative to patients who are allergic to penicillins. Analogs of erythromycin, like azithromycin, clarithromycin and dirithromycin, are more stable in acid and better in tissue distribution and also with less gastrointestinal side effects. Azithromycin and dirithromycin do not interact with the liver drug metabolizing enzymes as does erythromycin and thus do not have the same drug interactions. Development of these analogs was essentially driven by the need for drug with reduced side effects.

With the development of novel target directed screening procedures, discovery of antibiotics active against cell wall biosynthesis was possible in 1970s and 1980s. These included cephamycin, fosfomycin and thienamycin.
Indian Scenario

The Indian pharmaceutical industries are of Rs. 230 billion ($ 4.8 billion) in 2003 with a growth rate of 5%30. The average growth rate for the past 5 years has been around 10%. Fifty manufacturers share 80% of the market whereas rest is distributed amongst other formulation units. Alimentary and metabolic drugs lead the market followed by antiinfectives, respiratory, cardiovascular and musculoskeletal drugs (Table 7). Antifungicides are mature segments with nominal growth rates but are ‘cash cows’ of the market30. There are about 300 antibiotics currently available in Indian market under 1000 of brand names (Table 8). Semi-synthetic penicillin based formulation market (includes ampicillin and amoxycillin) accounts for nearly 25% of the total formulation market, is growing at a rate of 8-10% per annum (indiainfoline.com). The prices of intermediates for semi-synthetic penicillin have crushed in the last couple of years due to cheap imports from China. As a result, four domestic penicillin-G (Pen G) manufacturers are a baffled lot. These four companies are, J K Pharmachem Limited, Southern Petrochemicals Industries Corporation (Spic), Torrrent Gujarat Biotech Limited and Alembic Limited. Hindustan Max GB Limited (HMGB) was the highest producer of pen G in India. This company closed operations due to Chinese competition.

In the Indian pharmaceutical market, cephalosporins and combinations, broad spectrum penicillins and fluoroquinolones ranked as top three therapeutic classes. The cephalosporin market in India is estimated at around 1000 crore for the year 2002. Orchid Chemicals and Pharmaceuticals Ltd is the largest cephalosporin producer in India and has a 12% share in the global cephalosporin market. Aurobindo Pharma also has different cephalosporins in the market and it launched cefpirome, a fourth generation broad spectrum injectable cephalosporin, for the first time in India.

Conclusion

Several well-known antibiotics commonly used in healthcare have become ineffective as microbes develop resistance to them. The rate of mutation does not reciprocate with the discovery of antibiotics. Infectious microbes have a remarkable ability to evolve, adapt and develop drug resistance in an unpredictable and dynamic way. So the demand for effective antimicrobial compounds is growing rapidly and companies are trying to fill their pipelines with products that can meet the challenges of increasingly stubborn infectious agents. Also the large pharmaceutical companies, small biotech concerns and even many research institutions are in hunt for new weapons to meet the demand to fight troublesome microbial infections and are with several notable successes on the horizon.

References