Unmet Medical Needs and the Role of Pharmaceutical Companies

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1 Introduction

Rising health care costs have been prioritized in the budget planning of all Western countries. Rising R&D costs of up to $800 million per marketed new pharmaceutical have dramatically reduced the approval of new chemical entities (NCEs). Globalization of diseases like AIDS and SARS has had a definite impact on the economic situation not only in the Western world, but also in developing countries, especially for AIDS in Africa and SARS in Asia. The World Health Organization (WHO) is calling for free anti-tuberculosis (TB) drugs to be made available to people living with human immunodeficiency virus (HIV). The spread between unmet medical need in large indications (e.g. Alzheimer's disease) and in niche indications (e.g. Huntington disease) and the economic burden to create a blockbuster ($1 billion sales within one year after launch) has created a marketing-driven clinical development of new chemical entities. A paradigm shift has occurred by which developing a new innovative drug by documenting short-term efficacy, quality and safety rather than long-term efficacy and emphasizing pharmacovilliglance including considerations of health economy within the medical environment a shift that has fundamentally changed and challenged the pharmaceutical industry.

2 Challenge I: Globalization and Costs

Health costs in the Western world range as low as 6.9% of the gross domestic product in the UK to 13.1% in the USA followed by Germany with 12.3% with rising trends. In developing countries (especially in Africa) with almost no capital, health costs remain in the one-digit range and are almost negligible for medical care or prevention. Expenditures out of total health costs ranked number 3 in most countries and for medication range from as low as 11% in the USA to 13.3% in Germany to 16.3% out of the total health costs, demonstrating different policies and health environmental systems.

Unmet medical needs are a universal problem, affecting however different areas differently. While tuberculosis plays an increasing role in Asia (the number two cause of death in Indonesia) still cardiovascular diseases play a primary role in the civilized world though were overtaken by cancer in 2005.

S. Elm, S.N. Willich (eds.), *Quo Vadis Medical Healing,*

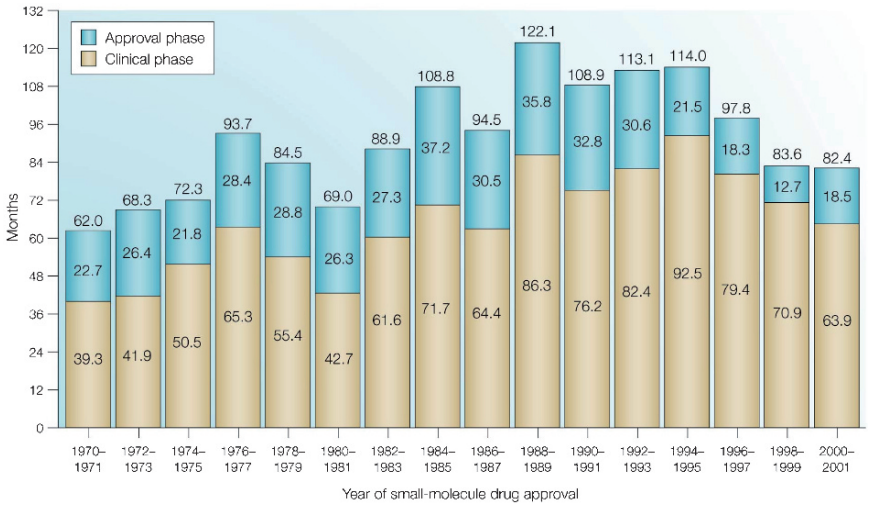

Fig. 1 Mean clinical and approval phase lengths for small-molecule drugs approved in the USA during 1970–2001 (Reichert 2003[12])

The share of the registered pharmaceutical world market demonstrated that more than 60% contribute to North America (especially the USA), 25% to Europe and more than 16% to Japan. The USA, therefore, is the main driver in pharmaceutical development.

In 1996, R&D costs were $16.9 billion, in 2002 at $32 billion; however, new chemical entities (NCEs) declined from annual $53 billion to $17 billion in the same time period. The mean clinical and approval phase lengths for small-molecular drugs approved have not changed in 30 years and will take – including preclinical development from CD (candidate drug) to NDA – approximately 12 years (Fig. 1).

3 Challenge II: Demographics and Patients

Demographics are changing due to life expectancy and GDP in different parts of the world (Fig. 2).

Africa, Asia and Australia, even growing by a two-digit percentage on the pharmaceutical market, contribute far less than 10% to the world market. Population-wise China with 1.3 billion people and a GDP of $4.8 billion contributes increasingly by volume not by value, but may be a main driver for new untreated population (e.g. approximately 40 million untreated asthmatic patients) and a growing pharmaceutical market, due to rising prosperity.

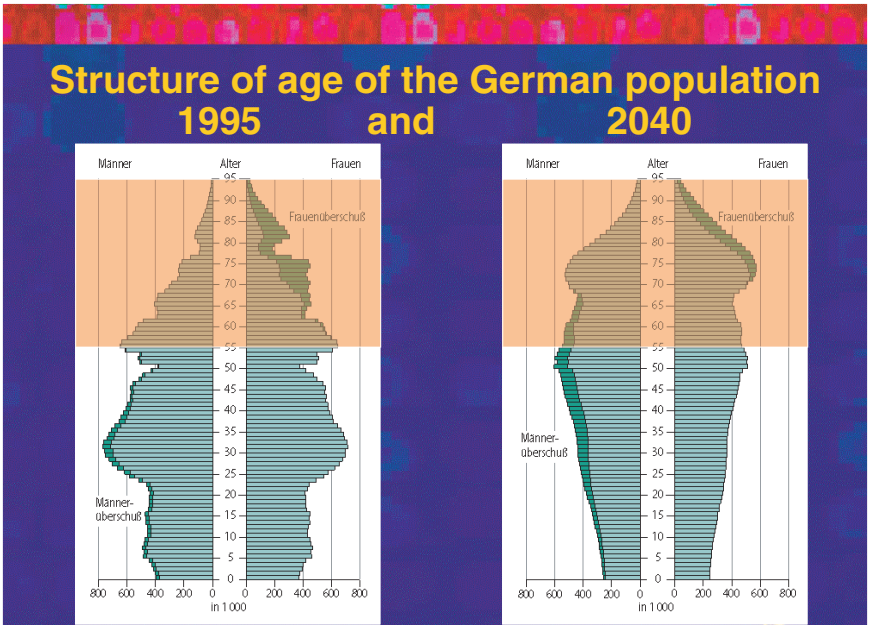

Fig. 2 Predicted demographic change in Germany

Demographic changes due to increasing life expectancy have altered the 'target population'. The unmet medical need for a population has broadened and shifted, e.g. for antibiotics for infectious diseases like syphilis, pneumonia, etc., to cardiovascular diseases at the end of the last century, whereas the most primary focus today relates to oncology, neuroscience and infection.

Pharmaceutical development has focused on the male population (due to the risk for women of childbearing potential) and on a target group of 20–60 years. Children and the growing elderly population have only poorly been investigated and off-label use is common.[1]

In the elderly population the most common neurodegenerative disease, Alzheimer's disease constitutes about two thirds of cases of dementia overall with vascular causes and other neurodegenerative diseases such as Pick's disease and diffuse Lewy-body dementia. Alzheimer's disease is a progressive neurological disease that results in the irreversible loss of neurons, particularly in the cortex and hippocampus and the clinical hallmarks are progressive impairment in memory, judgement, decision-making, orientation to physical surroundings, and language. Alzheimer's disease has a prevalence of approximately 1% among those 65–69 years of age and increases with age to 40–50% among persons 95 years of age and over.[2]

Parkinson's disease, the second most common neurodegenerative disorder after Alzheimer's disease, is clinically characterized by resting tremor, bradykinesia, rigidity

and postural instability, and pathologically by the loss of neurons mainly in the substantia nigra in association with the presence of ubiquinated protein deposits in the cytoplasma of neurons (Lewy bodies) and threadlike proteinaceous inclusions within neuritis (Lewy neuritis). Parkinson's disease has a prevalence of approximately 1% among persons 65–69 years of age, rising to 3% among persons 80 years of age and older.[3]

These diseases are predominantly idiopathic disorders of unknown pathogenesis. However, the genetic mapping and gene-isolation tools created by the Human Genome Project over the past decade have greatly accelerated the rate of identification of genes involved in the rare inherited forms of these diseases.

The Western world has changed its lifestyle; the estimated lifetime risk according to a recent US trial of developing diabetes for individuals born in 2000 is 32.8% for males and 38.5% for females. Females have higher residual lifetime risks at all ages. The highest estimated lifetime risk for diabetes is among US Hispanics (males, 45.4% and females, 52.5%). Individuals diagnosed as having diabetes have large reductions in life expectancy. A recent trial demonstrates that an individual diagnosed at age 40 will lose 11.6 life-years and 18.6 quality-adjusted life-years whereas women will even lose 14.3 life-years and 22.0 quality-adjusted life-years.[4]

On the other hand, the current statistics and outcome trials on cardiovascular diseases including acute myocardial infarction and ischemic heart disease have dropped continuously throughout the last decade due to better diagnostics, identifying risk factors and new medication including anti-hypertensives, anti-diabetics and thrombolytics.

4 Challenge III: Information and Education

Health data and literacy are a prerequisite for guided clinical development and the appropriate use of medication (81.5% of the total population in China compared to 52% in India) and have a huge impact on life expectancy (71.4 years in China and 62.5 years in India). The worldwide highest rate is currently in Japan with over 81 years for women and more than 75 years for men, which is comparable to the Western world.

Currently far more than 30% of patients in the USA first consult the internet before visiting a doctor and learn about web-based guidelines, trials and recommendations about the possible outcome of a disease.

The growing population of affluent older people may have greater expectations of medical care, fuelled by advertising and communication (older people are likely to demand cures for wrinkles, baldness, yellow teeth and relief from symptoms of menopause or andropause).

Botulinum toxin has been developed for the treatment of wrinkles, minoxidil for male pattern baldness (primarily developed as a vasodilating hypotensive drug), hormone replacement therapy, currently under heavy discussion for women, and Viagra for impotence developed as an anti-hypertensive drug. The limits to demand for health care have been widely discussed in the literature. The controversial results of the Women's Health Initiative Trial on post-menopausal hormonal treat-

ment (HRT) also published in the lay press have led to a 50% decrease according to a recently published observation in New Zealand.

The intrinsic prosperities of an 'ideal' drug cannot by themselves ensure appropriate utilization. An ideal treatment may enhance physician and patient comfort by providing maximum efficacy and safety in the most convenient formulation. This would entail once-daily administration of a single treatment not influenced by meals or time of day with no adverse event or monitoring required, no adjustment for age, weight or race. Therefore comprehensive leaflets or programmes of effective communication and educational tools are necessary. Huge armies of representatives distribute such information, but have been heavily criticized for the only minutes-lasting information given to the doctor. However, in general licensed doctors do not have to update their knowledge on pharmacotherapy on an obligatory basis and rely on the information and education provided by the pharmaceutical industry.

5 Challenge IV: Evidence-Based Medicine and Medical Marketing

Almost all of the ten biggest pharmaceutical companies in the world have at least two cardiovascular drugs in their pipeline or in their portfolio. Anti-hypertensives like beta blockers, angiotensin II antagonists and calcium antagonists sales have been rising throughout the years, since better diagnostic tool awareness and communication of risk factors documented by international megatrials and huge prospective outcome studies have been communicated via lay press and internet within and without the industrialized world.

6 Challenge V: Diagnostics and Prognostics

Simple screening diagnostic tools like blood pressure measurements and blood sugar cholesterol have changed and have been included in the guidelines for medication. New individual or conventional prognostic factors may even build up a different understanding in the pathogenesis of a disease and may ameliorate standard treatment to be documented in outcome trials. More than 50% of patients with coronary heart disease (CHD) lack any conventional risk factors (cigarette smoking, diabetes, hyperlipidemia and/or hypertension).[5]

Among patients with CHD at least 1 of 4 conventional risk factors was present in 84.6% of women and 80.6% of men. Other non-traditional factors and genetic causes have to be evaluated. Although C-reactive protein (CRP), lipoprotein (A), fibrinogen and homocysteine are associated with vascular risk, their optional use in routine screening and risk stratification remains to be demonstrated.[6]

The introduction of CAD risk equivalent categories within the American ATP III Guidelines substantially increases the number of patients eligible for LDL-cholesterol

reduction to less than 100 mg/dl from approximately 5 or 6 million to approximately 20 million. More intensive lipid modifying treatment is thus also clearly needed to provide the additional reduction LDL-cholesterol methods for achieving optimal levels in patients with more challenging LDL-cholesterol goals. Prospective observational studies identified low HDL cholesterol as an important independent coronary risk factor. Some rare inborn errors of HDL metabolism cause low HDL cholesterol and premature atherosclerosis. In large, controlled intervention studies, statin and fibrate treatment of patients with increased HDL cholesterol reduced the incidence of coronary events, and in some of these trials, the increase in HDL cholesterol correlated significantly with the decrease of event rates. HDL-associated proteins and lipids exert several potentially anti-atherosclerotic activities. Transgenic over-expression of human apoA-I or ABCA1 genes was shown to inhibit the development or even induce regression of atherosclerosis in atherosclerosis-susceptible animal models.

Six controlled and perspective landmark studies (>50,000 patients >5 years) demonstrated that lowering of LDL cholesterol with HMA-CoA reductase inhibitors (= statins) or fibric acid derivatives (= fibrates) therapy reduces coronary event rates by 30% (fatal and non-fatal MI, as well as coronary intervention).[6–7] LDL is currently considered a causal factor (and main diagnostic tool) in atherosclerosis, but may be just the tip of the iceberg, whereas the pleiotropic effects of statins may also cover other effects, e.g. anti-inflammatory and antifibrotic potencies.

7 Challenge VI: Drug Design and Individual Therapy

Traditional progress to cancer treatment relies on the combination of surgery, radiotherapy and chemotherapy. Current cancer drugs which are mostly lethal for cells (cytotoxics) either affect DNS synthesis and the process of cell division or cause chromosomal damage. Identifying a candidate drug (DC) via computer, chemical or biotechnical models followed by *in vitro/in vivo* proof of concept will lead to a new chemical entity (NCE). Biotechnical engineering in the production of new drugs plays an increasing and important role (e.g. STH, insulin, TPA), the role of gene therapy is yet limited to well-defined niche indications and will not revolutionize the pharmaceutical world but will affect approximately 20% of the diseases within the next two decades. Which population will be targeted and who can pay for it or provide reimbursement will have a major impact on the success of individualized or gene therapy in the near future.

8 Challenge VII: Patent and Generics

The life cycle of a new pharmaceutical has a great impact on investment for the pharmaceutical industry. An innovation of changing salicylate into acetylsalicylate has been developed in the early last century, but the pathophysiological pathways have only been evaluated within the last decades including anti-thrombotic effects, stroke prevention and even anticancer potentials. Nevertheless, aspirin is out-of-patent

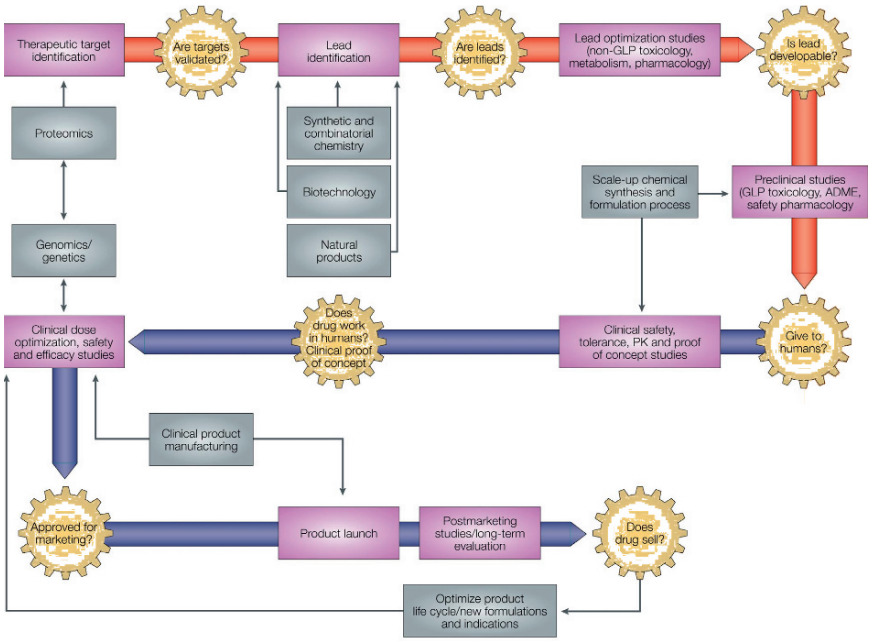

Fig. 3 Process of drug development (Pritchard et al. 2003[13])

for decades and only different formulations may protect the originator from overrun by generics or even OTC (over-the-counter) medication. The patent situation in different countries might be the key to success or a nightmare for a pharmaceutical company because development times reach up to 10–12 years before being approved by the authorities or even marketed. Despite improving clinical development but due to the increasing prerequisites guidelines to develop a new pharmaceutical, it has left normally only a couple of years for new pharmaceuticals to pay back the huge development costs of approximately $500–800 million. Different national laws allow different patent interpretations, whereas molecule patent or manufacturing patents are differently interpreted, indication patents are almost not valid outside the USA.

Today the biggest market of more than $21 billion in 2002 are the statins, which have been proven to prevent coronary heart disease (CHD).[6–8] The situation that statins were claimed to have hypothetically an anti-osteoporotic effect and being patented by an American company has led to a reduced interest in the pharmaceutical industry to develop this indication because royalties would have to be paid to the appropriate patent holder and outcome trials demonstrating superiority will last more than 5 years with 10,000 patients in different populations and a high risk of failure.

Generics are quite necessary to reduce costs and stimulate innovations. The current situation, however, demonstrates an increasing share of generics, especially in countries

like Germany or Denmark which face a generic market of more than 50%, whereas in the USA (currently heavy discussion about import from outside especially Canada and Mexico), the UK and France this market is yet in the range of 10%. The existence of generics on the one hand has built up a whole new industry with two-digit growth taking market share and volume with no money spent on innovation or any clinical development. The pharmaceutical companies on the other hand spend up to 20% of their sales on R&D development. The different legislations within the different countries in Europe also have built up parallel trade to undermine the bright politics earning in the range of billions for a parallel trader who just repacks, refills and sends it to different countries.

9 Challenge VIII: Health Care and Lifestyle Medicine

The development of sildenafil for erectile dysfunction, orlistat for obesity and minoxidil for male pattern baldness have been classified as "lifestyle drugs" in the popular imagination.[9] It is difficult to define what we mean by the term lifestyle drug since the perception of what is illness and what is within the sphere of personal responsibility rather than health care may depend on whether one is a potential patient or potential payer, thus problems at the margins of health and well-being.[10]

10 Conclusions

The pharmaceutical industry is an important economic tool in the Western world. The increasing costs of health care systems in any country in the world have recently changed the paradigm from developing a new, efficacious and safe high-quality drug for unmet medical need to identifying either potential blockbusters or individual biotechnically driven, highly specialized individual therapies. The main cost drivers are still the treatments of the most common diseases like cardiovascular, oncological or infectious diseases.

In the early 1990s, the Australian government introduced formulary submission guidelines[11] and since then such guidelines have been applied in many major markets. The need to demonstrate cost-effectiveness, affordability and the benefit–risk ratio to the health system of a preferred formulary position as opposed to a restricted indication, where the product is targeted at subpopulation of patients is leading into off-label use.

The efforts to develop an innovative drug to be competitive, well-tolerated and reimbursed by the different health insurance systems have become as costly as a more than $500-million jigsaw puzzle which may pay off in the case of statins and proton pump inhibitors.

The failure or safety issue may delete or seriously effect a worldwide operating company as seen 30 years ago in the case of Grünenthal (thalidomide) or recently for Bayer (cerivastatin: Lipobay).

The probabilities for success or forecasting are not real science but have made development of medication a risky business case for any unmet medical need.

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