

Il rapporto tra medicina generale e farmaci innovativi

Ovidio Brignoli
MMG.Brescia

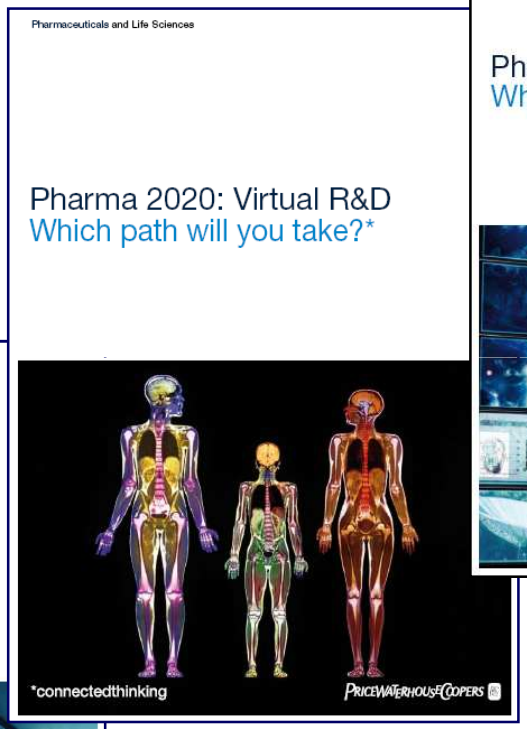
Il rapporto tra MG e farmaci innovativi

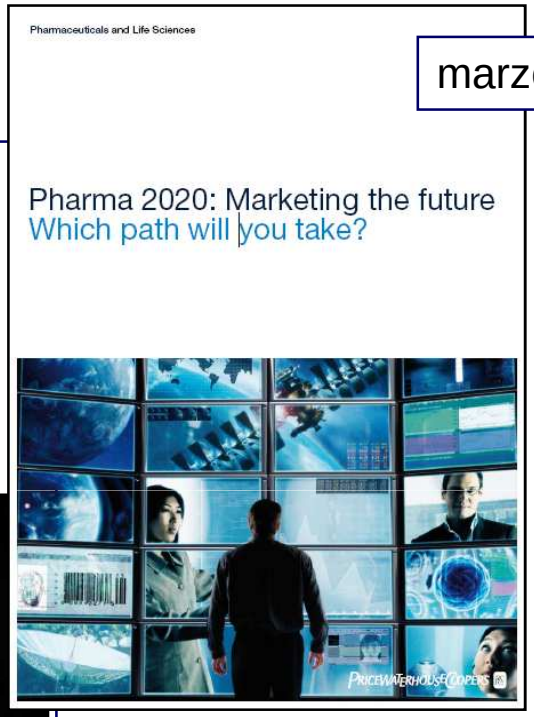
- Evoluzione 2009 – 2012
- Innovazione Terapeutica
- MG e farmaci innovativi

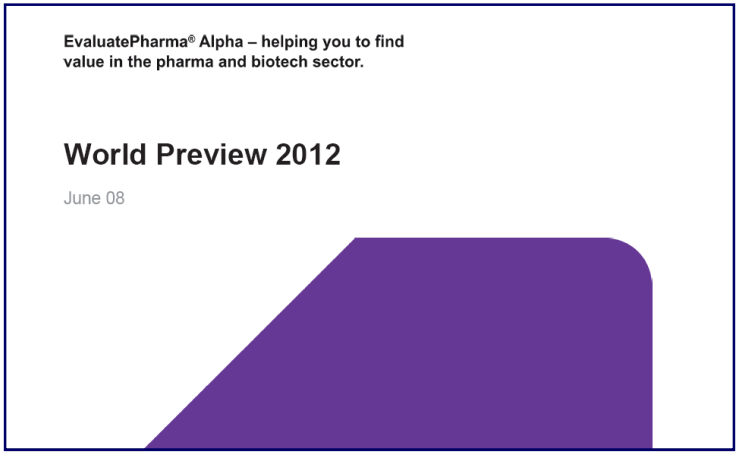
Evoluzione 2009 - 2012

marzo 2009









Evoluzione 2009 - 2012

- ***Generic Cliff***
  - Scadenze brevettuali
- **Produttività RD**
- **Evoluzione della Sanità**
  - Innovazione & Valore
    - Value-based Pricing
    - Pay-For-Performance

EDITORIAL

Perspectives on the "Generic Cliff"—Pushing and Falling

Frederic R. Curtiss, PhD, RPh, CEBS

Wall Street health sector analyst Tim Anderson, MD, now at BernsteinResearch, called it the "generic cliff" in early 2007.[1] From the perspective of brand-name pharmaceutical manufacturers and investors, the generic cliff is indeed formidable and often foreboding. What was a relatively gentle slope in erosion of the brand share of days of drug therapy when generic ranitidine entered the market in 1997, became steeper in August 2001 with generic fluoxetine (Prozac), and steeper yet with generic citalopram (Celexa) in November 2004 and generic simvastatin (Zocor) in July 2006 (Figure). For managed care organizations (MCOs), the generic cliff is a gold mine with a huge opportunity to increase the generic dispensing ratio (GDR) for individual drugs and for therapeutic classes through therapeutic selection.

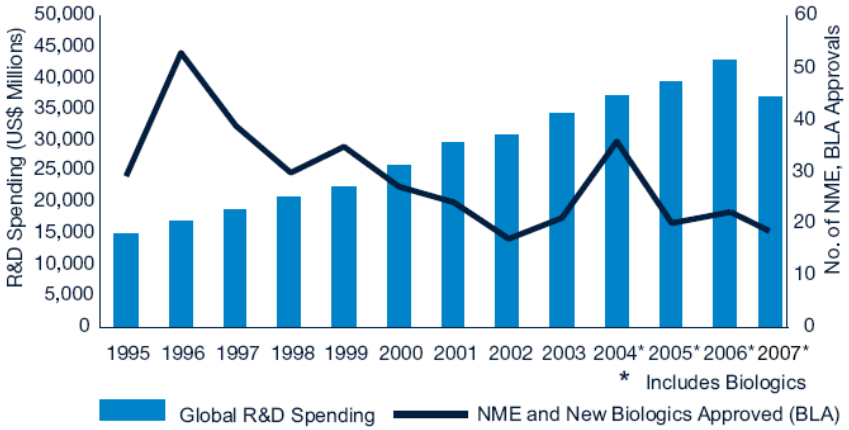
MCOs have used physician and member financial incentives to increase GDRs, and thereby reduce the drug cost per therapy. BCN and $1 million in lower (generic) copayments for members. Other health plans such as Excellus BCBS in upstate New York use physician-incentive programs to achieve increases in GDRs, and the GDR is evolving as a fundamental measure in physician pay for performance (P4P).[6]

MCOs and employers have also found success in step-therapy programs and pharmacy benefit designs that impose maximum allowable costs by therapeutic indication. For heartburn for example, a therapeutic maximum allowable cost (TMAC) per day of drug therapy was found to produce savings per day of more than 80% and net savings per member per month (PMPM) of more than 90% for the drug plan sponsor.[7] Admittedly, TMAC is limited to therapeutic classes such as drugs for heartburn, where there is little if any controversy about the interchangeability of therapeutic alternatives to obtain the same clinical outcome (relief of heartburn with comparable safety).[8]



Evoluzione 2009 - 2012

- ***Generic Cliff***
  - Scadenze brevettuali
- **Produttività RD**
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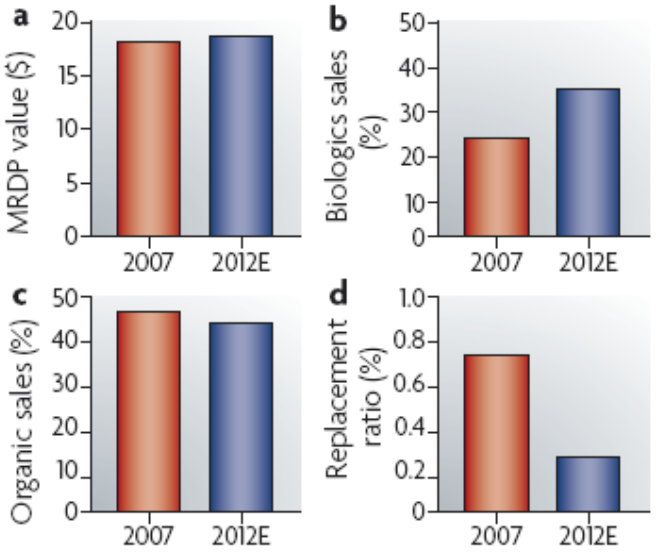


Figure 1 | **Selected pharma industry metrics 2007–2012E.**

Evoluzione 2009 - 2012

- *Generic Cliff*
  - Scadenze brevettuali
- **Produttività RD**
- **Evoluzione della Sanità**
  - Innovazione & Valore
    - Value-based Pricing
    - Pay-For-Performance



Pay drug firms by their results, say Tories

By Robert Winnett
Deputy Political Editor

DRUG companies would only be paid by the NHS if their treatments improved a patient's health, under plans unveiled today by the Conservatives.

The National Institute of Health and Clinical Excellence (Nice), which has been accused of failing patients by barring potentially life-saving drugs, should introduce a system of "payment by results", the Tories say. The proposal, part of an overhaul of the drug rationing system, is made in an online article for *The Daily Telegraph* by Andrew Lansley, the shadow health secretary. He claims the current system is "tragically" cutting people's lives short.

Nice evaluates drugs on their "cost-effectiveness" and drugs because they say it's not cost-effective – as Nice has done recently with four kidney cancer drugs – we should encourage the NHS to use new medicines which are clinically effective and agree subsequently to pay the drugs companies according to the therapeutic benefit.

"In other words, drugs companies should only be paid according to the benefits that a drug brings to patients."

He added: "Nice should be involved in this process, working with drug companies to set fair prices for new medicines – rather than refusing new treatments which it deems too expensive."

Mr Lansley says there are already small-scale examples of drugs companies agreeing to be paid for the drug only where it has been successful.

"At the moment everyone loses out – patients don't get new and potentially life-saving drugs, the NHS can't innovate and meet the needs of patients, and drugs companies don't get the opportunity to introduce their new therapies," said Mr Lansley.

"Every time a patient dies having been denied a new drug which should be available to them it is a tragedy.

"The Government should act swiftly now to reform the system before any more people's lives are tragically cut short." The Conservative proposals, to be set out in a speech by Mr Lansley to the CBI today, are likely to be welcost and several have begun high-profile court cases to challenge decisions.

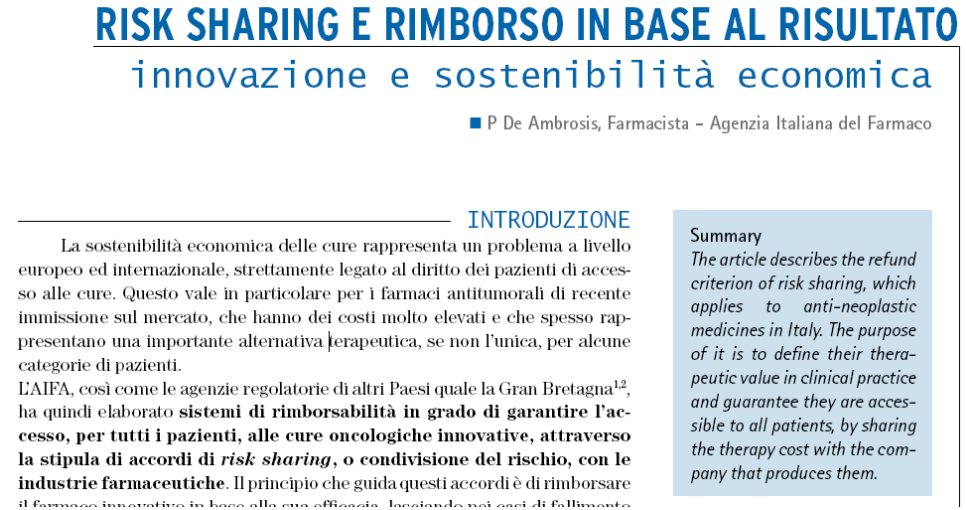
Drug companies are also growing increasingly frustrated by what they regard as an inflexible and time-consuming approach to approving new treatments.

Nice looks at whether drugs are cost-effective for the NHS with the maximum for any one treatment capped at between £20,000 and £30,000 per person per year.

It has barred some treatments for kidney diseases, Alzheimer's, multiple sclerosis and arthritis.

Many patients lost their sight after Nice took two years to approve a new treatment for blindness.

Dialogo sui farmaci • n. 5/2008 POLITICA SANITARIA < 235



RISK SHARING E RIMBORSO IN BASE AL RISULTATO

innovazione e sostenibilità economica

■ P De Ambrosis, Farmacista – Agenzia Italiana del Farmaco

INTRODUZIONE

La sostenibilità economica delle cure rappresenta un problema a livello europeo ed internazionale, strettamente legato al diritto dei pazienti di accesso alle cure. Questo vale in particolare per i farmaci antitumorali di recente immissione sul mercato, che hanno dei costi molto elevati e che spesso rappresentano una importante alternativa terapeutica, se non l'unica, per alcune categorie di pazienti.

L'AIFA, così come le agenzie regolatorie di altri Paesi quale la Gran Bretagna[1,2], ha quindi elaborato **sistemi di rimborsabilità in grado di garantire l'accesso, per tutti i pazienti, alle cure oncologiche innovative, attraverso la stipula di accordi di *risk sharing*, o condivisione del rischio, con le industrie farmaceutiche**. Il principio che guida questi accordi è di rimborsare

Summary

The article describes the refund criterion of risk sharing, which applies to anti-neoplastic medicines in Italy. The purpose of it is to define their therapeutic value in clinical practice and guarantee they are accessible to all patients, by sharing the therapy cost with the company that produces them.

Il rapporto tra MG e farmaci innovativi

- Evoluzione 2009 – 2013

- Innovazione Terapeutica

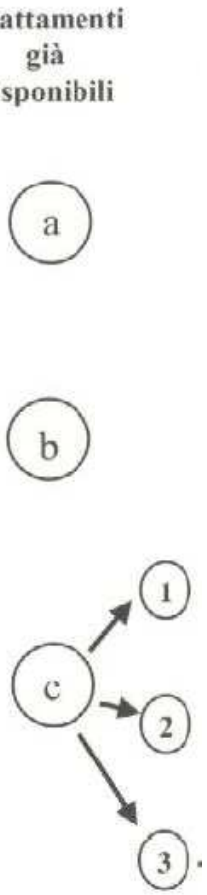
- MG e farmaci innovativi

Valutare la Innovazione Terapeutica

malattie orfane di terapia

bisogno / rischio residuale

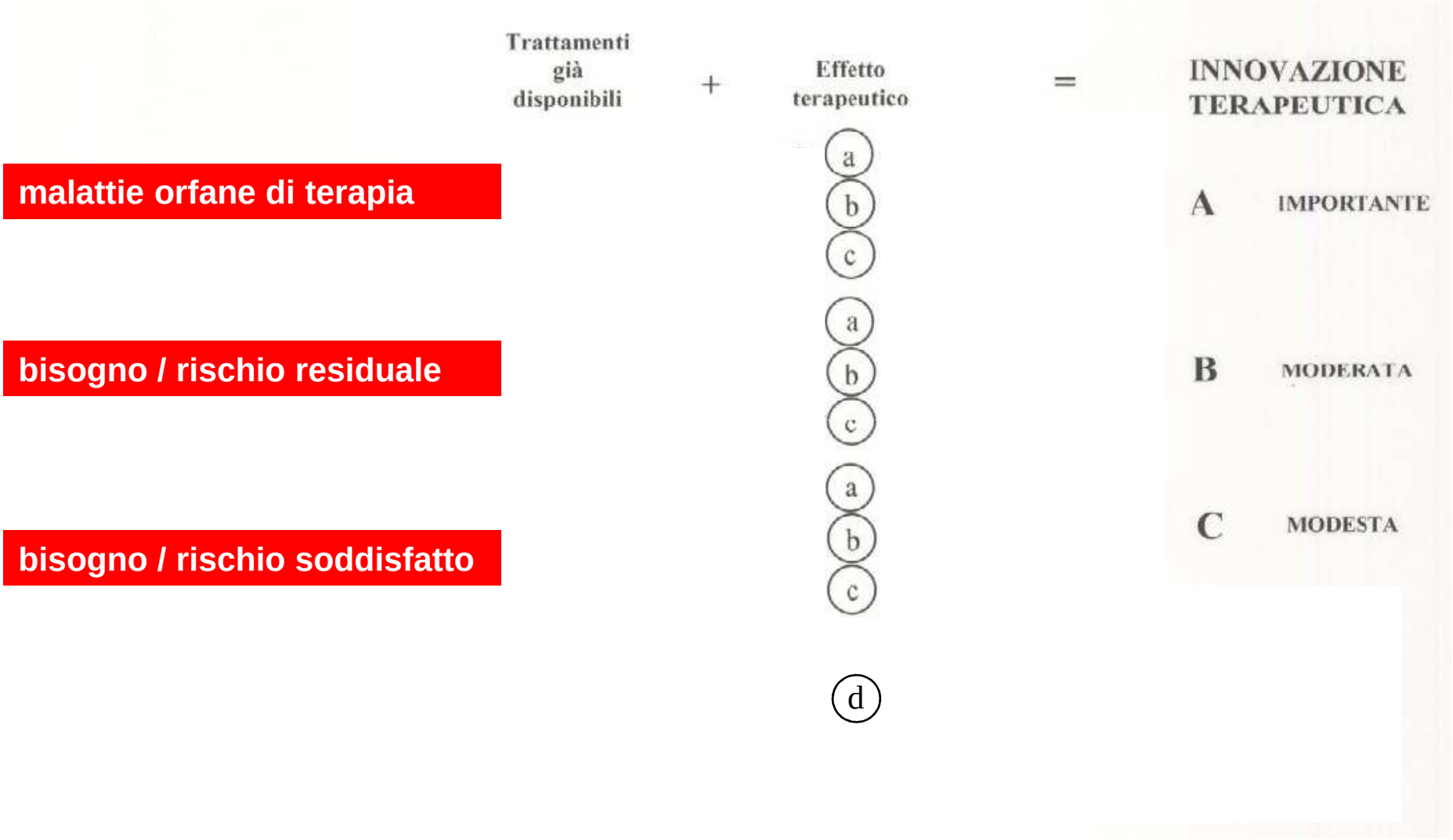
bisogno / rischio soddisfatto



INNOVAZIONE TERAPEUTICA	
A	IMPORTANTE
B	MODERATA
C	MODESTA

AIFA 2007 - 2008

Valutare la Innovazione Terapeutica



malattie orfane di terapia

bisogno / rischio residuale

bisogno / rischio soddisfatto

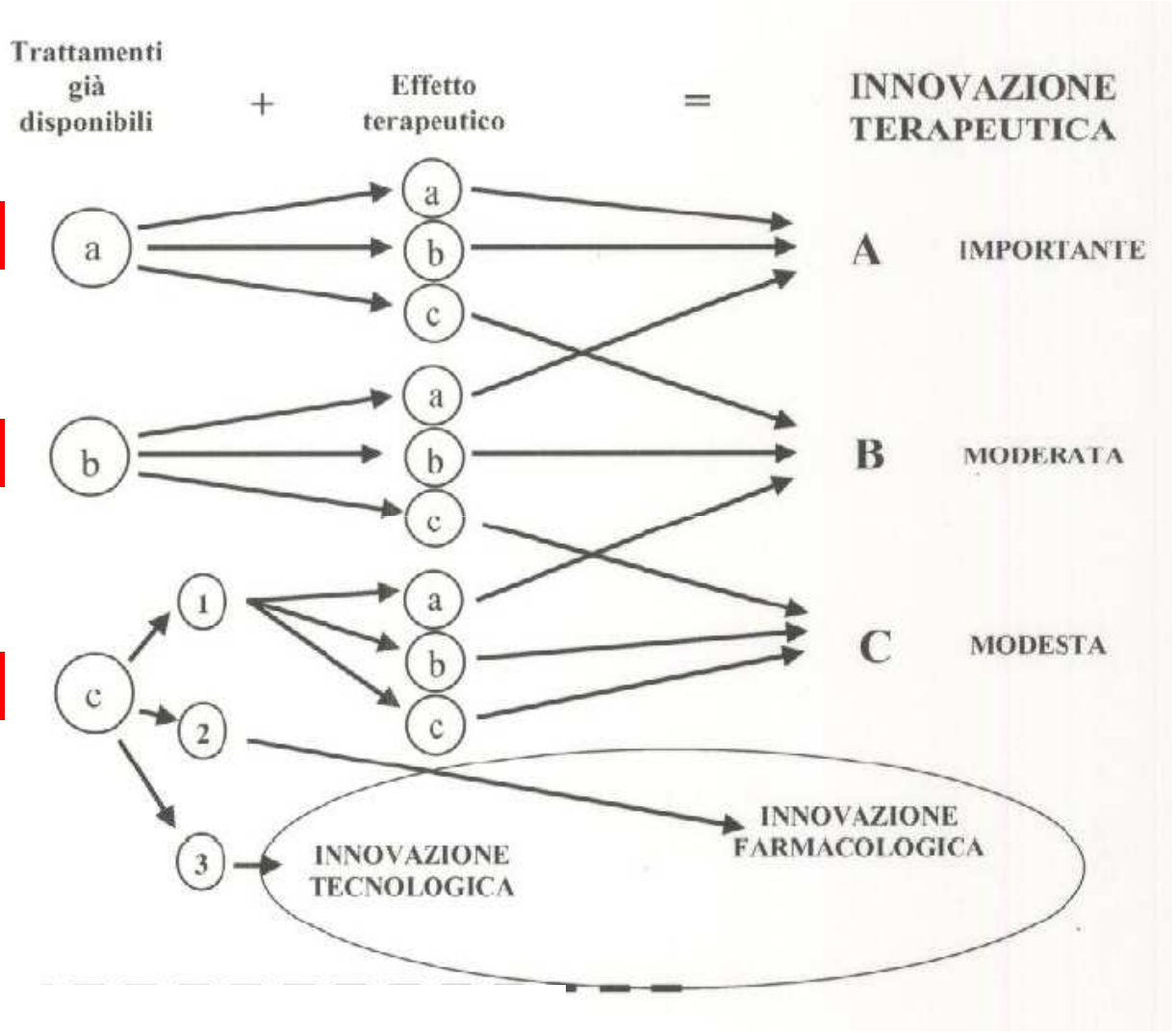
AIFA 2007 - 2008

Valutare la Innovazione Terapeutica

malattia orfane di terapia

bisogno / rischio residuale

bisogno / rischio soddisfatto



AIFA 2007 - 2008

Progettare la Innovazione Terapeutica

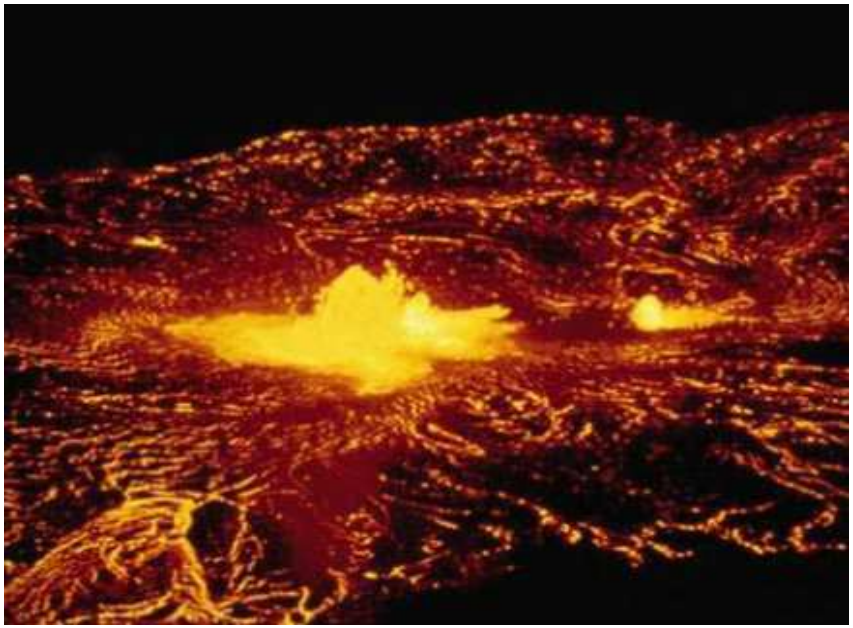
- **Indicazioni**
  - bisogni assoluti
  - bisogni residuali
- **Popolazioni**
  - selezionate
- **Variabili**
  - rilevanti
- **Confronti**
  - terapia di riferimento
  - superiorità

Pharmaceutical Executive
Advancing business leadership
europe

Beyond the Blockbuster: What Can Big Pharma Learn from Mid-tier and Specialty Pharma?

Gerhard Symons, *Pharmaceutical Executive Europe*, May 2008

Mounting evidence suggests that the big pharmaceutical companies should change their R&D and business models if they are to compete with mid-tier and specialty companies in search of value. So what are the lessons Big Pharma can learn from the way its smaller rivals do business?



Che cosa c’è dietro la porta?

- Biologia
- Immunologia

- Genomica
  - Farmacogenomica
  - Farmacogenetica

- Anticorpi Monoclonali
- Vaccini ed Adiuvanti

CYTOKINES AND AUTOIMMUNITY

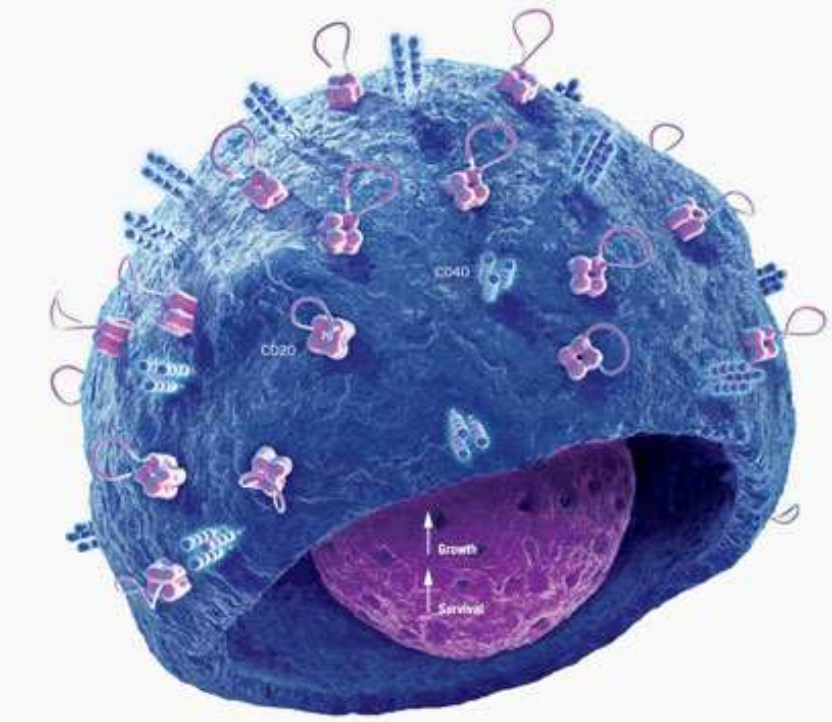
John J. O'Shea, Averil Ma‡ and Peter Lipsky**

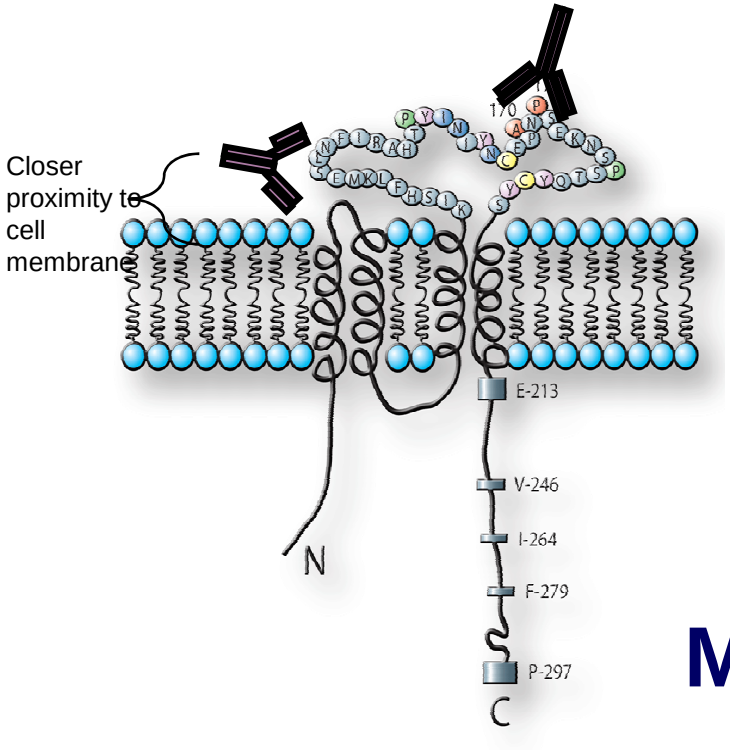
Cytokines have crucial functions in the development, differentiation and regulation of immune cells. As a result, dysregulation of cytokine production or action is thought to have a central role in the development of autoimmunity and autoimmune disease. Some cytokines, such as interleukin-2, tumour-necrosis factor and interferons — ostensibly, the 'bad guys' in terms of disease pathogenesis — are well known for the promotion of immune and inflammatory responses. However, these cytokines also have crucial immunosuppressive functions and so, paradoxically, can also be 'good guys'. The balance between the pro-inflammatory and immunosuppressive functions of these well-known cytokines and the implications for the pathogenesis of autoimmune disease is the focus of this review.

Autoimmune diseases, which affect approximately 5% of the population and disproportionately affect women, comprise a heterogeneous group of poorly understood disorders[1,2]. In general, these illnesses are characterized by the presence of abnormal lymphocyte activation, although we now know that non-lymphoid cells, especially antigen-presenting cells such as macrophages and dendritic cells (DCs), also have will also draw on lessons learned from interferons (IFNs) and tumour-necrosis factor (TNF) to illustrate these points.

A simple, but flawed, view of cytokines

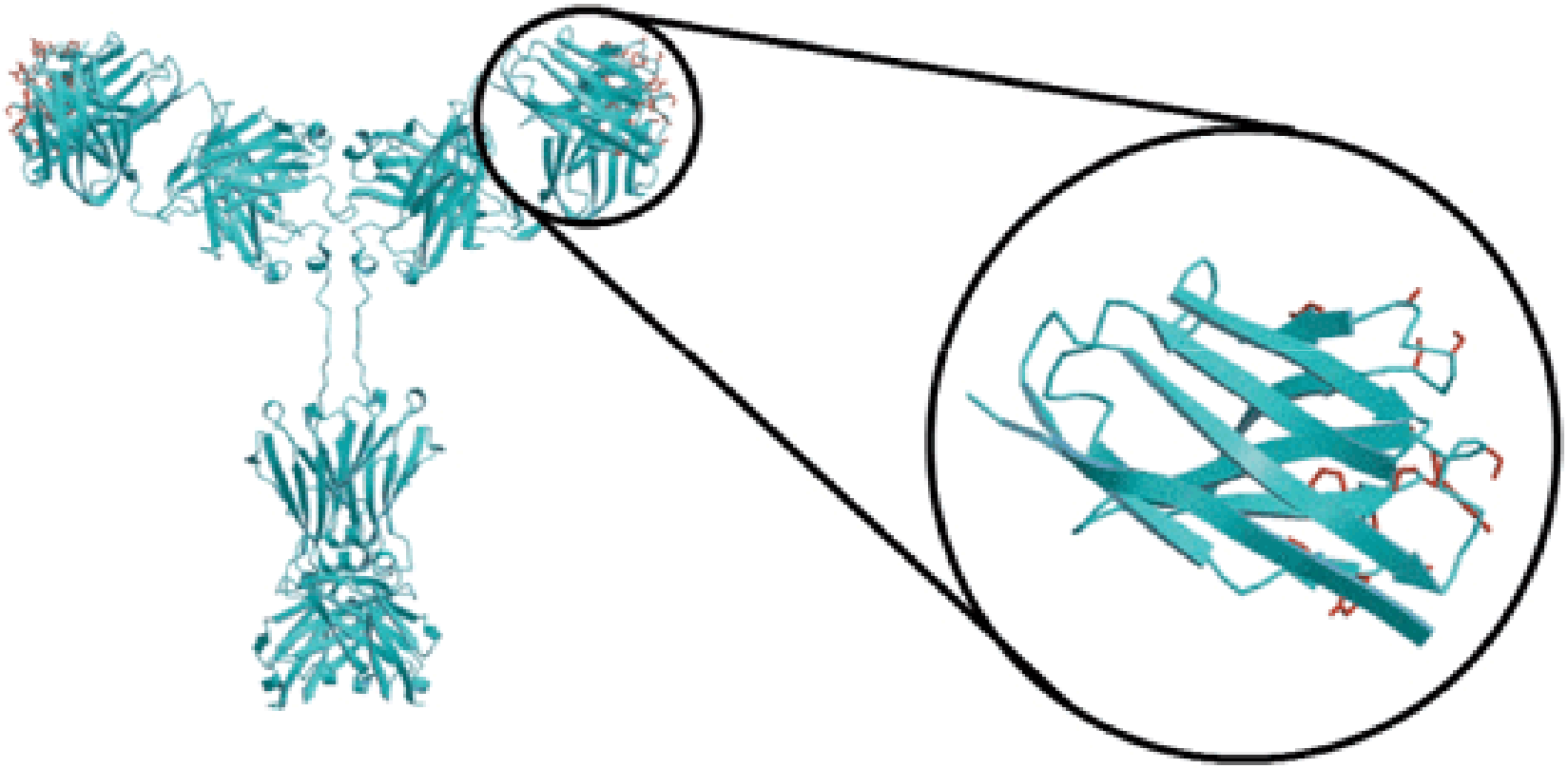
It is recognized that T-lymphocyte function contributes to the pathogenesis of many autoimmune diseases. The accepted model is that naive T cells become activated by





Mab

Domain Antibodies – 2^ Generazione Mab



IgG
(MW 150 kD)

dAb
(MW 11-13 kD)

Vaccini ed Adiuvanti oltre i microorganismi

nature publishing group

EDITORIAL

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 82 NUMBER 6 | DECEMBER 2007

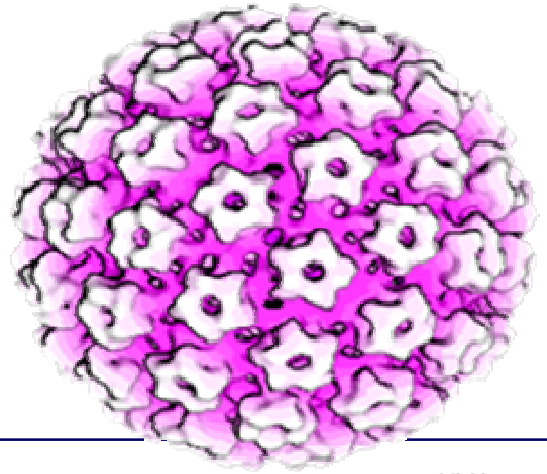
Pharmacology, Vaccinomics, and the Second Golden Age of Vaccinology

GA Poland[1]

"The great thing in this w
where we stand, as in wh
moving."

Olive

Clinical pharmacology an



DEVELOPMENT

nature publishing group

Vaccine Immunopotentiators of the Future

VEJC Schijns[1] and WGJ Degen[1]

Vaccine adjuvants or immunopotentiators comprise a diverse group of molecules or formulations. Despite a wealth of different candidates, there is a need for better vaccine adjuvants in both veterinary and human medicine. For human vaccines, the immunopotentiator choice has been limited to aluminum salts, until recently. By contrast, a whole range of adjuvants is employed for inactivated veterinary vaccines, due to less stringent safety and regulatory requirements and proven superior vaccine performance. This

Toll-like receptor-4 (TLR-4) for lipopolysaccharide, a well-known immunity activator. The finding that dendritic cells act as essential and superior antigen-presenting cells for primary immune reactions by Steinman and Banchereau[6] also proved a hallmark in immunology, enabling studies focused on critical steps in antigen presentation.

All these new insights fueled the desire to design vaccines rationally, based on science and less on serendipity or trial and error. Ideally, vaccine design begins with knowledge

- **Ipertensione**
- **Alzheimer**
- **Cocaina**
- **Nicotina**
- **Neoplasie**

Vaccini ed Adiuvanti oltre i microorganismi

BIOBUSINESS BRIEFS

TRIAL WATCH

Progress for Phase III cancer vaccines

Non-Hodgkin's lymphoma. Biovest International has recently reported that data from a randomized, controlled Phase III trial show that the cancer vaccine BiovaxID significantly prolongs cancer-free survival for patients with follicular non-Hodgkin's lymphoma. The intent-to-treat analysis ($n = 117$) showed a median duration of 44.2 months cancer-free survival with BiovaxID compared with 30.6 months in the control group ($p = 0.045$).

The Phase III trial of BiovaxID, a personalized subcutaneous anti-idiotype vaccine combined with granulocyte–macrophage colony stimulating factor, was closed earlier this year when interim trial results reviewed by an independent data monitoring committee

Renal cancer. Oxford BioMedica announced in October this year that the FDA has agreed a series of protocol amendments for their Phase III TRIST study of TroVax — a gene-based tumour vaccine that uses a modified poxvirus vector to deliver the tumour-antigen gene *5T4* and induce an anti-5T4 immune response — in renal cancer. The vaccine is being developed in collaboration with Sanofi–Aventis.

Earlier this year, analysis of the ongoing TRIST study by an independent data safety management board resulted in the recommendation that the trial should continue but that further vaccinations should stop. The preliminary analysis suggested that less than 13 doses of TroVax may be



and Immunology and Director of the Dodson Interdisciplinary Immunotherapy Institute, University of Miami, USA, thinks that a shift in

Farmacogenetica

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

N ENGL J MED 358;10 WWW.NEJM.ORG MARCH 6, 2008

Pharmacogenetics – Ready For Prime Time?

Susan B. Shurin, M.D., and Elizabeth G. Nabel, M.D.

It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter.

— FDA-approved labeling for warfarin (Coumadin) NDA 9-218/5-105

of drugs to guide prescribing decisions for agents currently on the market. Indeed, it is not much of a stretch to imagine that someday soon DNA sequencing will be a routine part of the workup for patients, at the very least to identify a patient's sensitivity to drugs that are likely to produce adverse effects.

Farmacogenetica

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

N ENGL J MED 360;8 NEJM.ORG FEBRUARY 19, 2009

Pharmacogenetics — Tailoring Treatment for the Outliers

Janet Woodcock, M.D., and Lawrence J. Lesko, Ph.D., F.C.P.

If it were not for the great variability among individuals, medicine might as well be a science and not an art.

— Sir William Osler (1892)

Over the past half century, biomedical science has developed randomized, controlled clinical-trial methods that can distinguish treatment effects from the noise of human variability. Positive results from tests of a treatment in a randomized, controlled trial provide great confidence that an intervention improves a prespecified outcome in a population defined by explicit entry criteria. These methods are rightly venerated because they have helped move medicine from anecdote to science and have largely brought about the ther-

patients who required therapeutic anticoagulation.[1] For each patient, the investigators identified the stable warfarin maintenance dose that resulted in the desired therapeutic international normalized ratio (INR). The range of doses that were needed to achieve the target pharmacodynamic effect in this large, geographically diverse cohort is shown in Figure 1. The investigators found that doses predicted by a pharmacogenetic algorithm — one that included both clinical and genetic factors — were better correlated with the empirically determined maintenance doses than were those predicted by a clinical algorithm; both algorithms outperformed a standard dose of 5 mg per day. However, this improvement was not spread equally across the population. For the 54% of people in the middle of the range, the algo-

Test predittivo	Indicazione	Produttore	Prezzo
deCODE T2™	Diabete	deCode Genetics	500 US$
deCODE AF™	Fibrillazione striale	deCode Genetics	ND
BRACAnalysis®	Carcinoma ereditario della mammella e dell'ovaio	Myriad Genetic Laboratories	ND
COLARIS®	Carcinoma nonpoliposico colorettale ereditario	Myriad Genetic Laboratories	ND
COLARIS AP®	Carcinoma e poliposi adenomatoda famigliare del colon	Myriad Genetic Laboratories	ND
MELARIS®	Melanoma ereditario	Myriad Genetic Laboratories	ND
Celiac Disease DNA		Genelex	445 US$
Hemochromatosis DNA		Genelex	395 US$
MammaPrint®	Rischio di metastasi in pazienti con carcinoma mammario	Agendia	ND
FAMILION® test	Canalopatie cardiache comprese Sindrome QT Lungo (LQTS) e Sindrome di Brugada	Clinical Data, Inc	ND

Il rapporto tra MG e farmaci innovativi

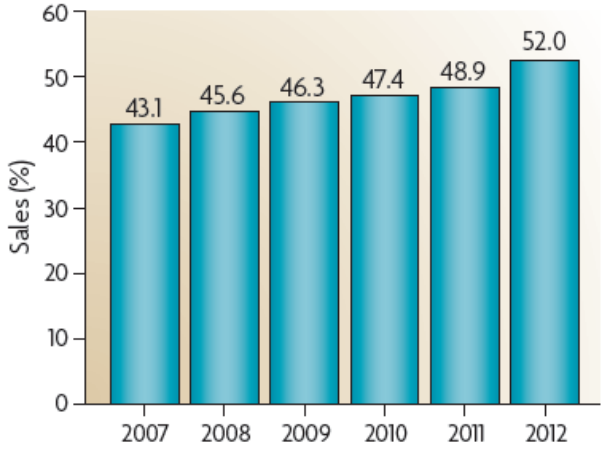
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MG e farmaci innovativi

BIOBUSINESS BRIEFS

MARKET WATCH

Specialty pharmaceuticals to provide majority of sales by 2012



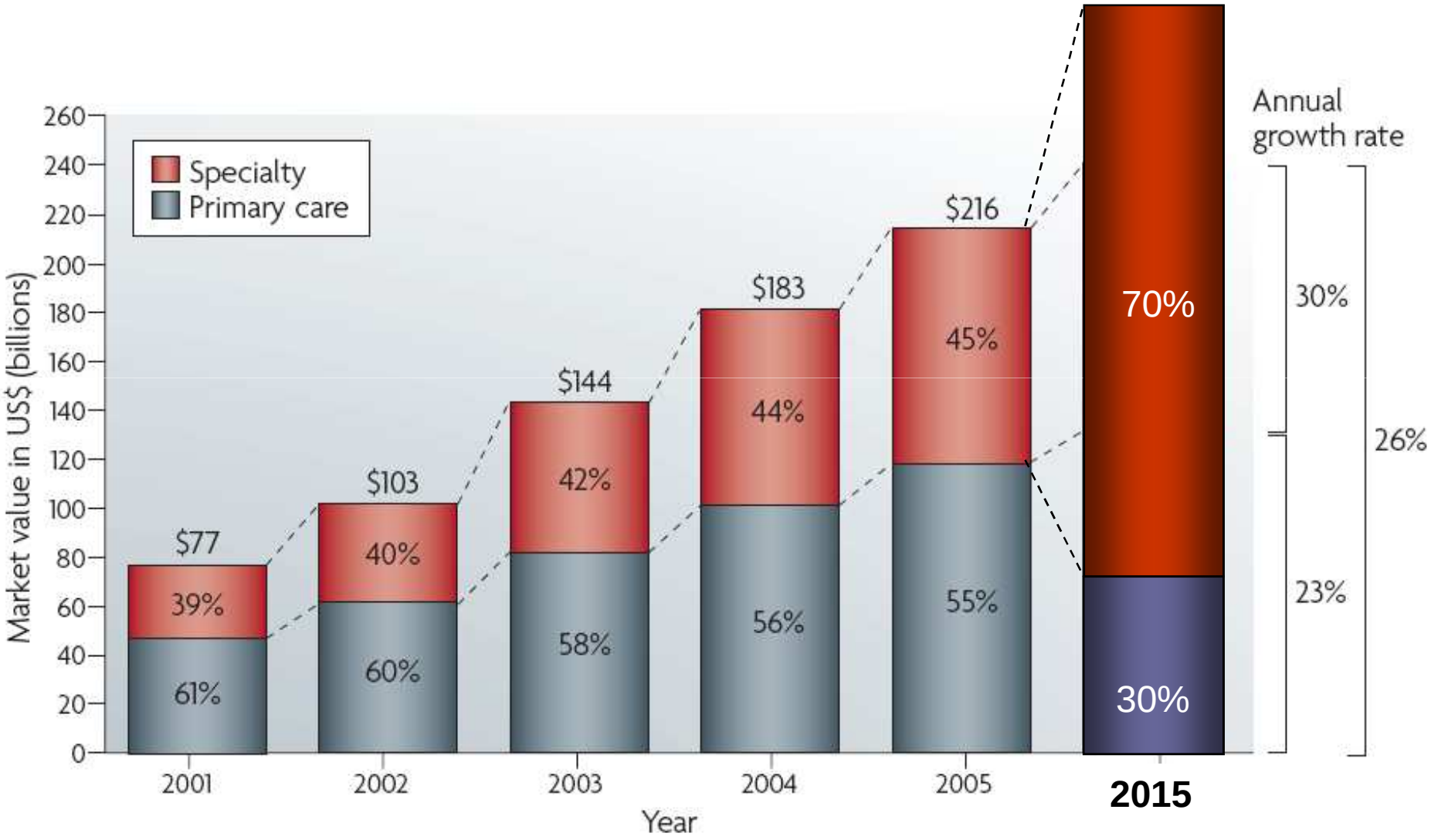
Large pharmaceutical companies have increasingly been pursuing specialty pharmaceuticals — that is, drugs prescribed primarily by specialists rather than general practitioners (GPs). To investigate this trend, AVOS Life Sciences have analysed the performance of the top 14 pharmaceutical companies with respect to the overall group's average share of portfolio sales derived from specialty products. For this we used consensus investment research that has been processed to allow systematic analysis (see Supplementary information S1 (box)). The analysis focuses on each company's major Rx drug portfolio

bevacizumab (Avastin; Genentech/Roche), which together are predicted to generate over $16 billion in sales in 2012. Company performance varies widely: for example, Roche and Amgen are expected to derive 92% and 88%, respectively, of MRDP revenue from specialty drugs in 2012, whereas for Sanofi–Aventis and Merck these figures are only 16% and 7%, respectively.

The group of US companies is predicted to achieve an average of 55% of portfolio sales from specialty products, compared with 48% among the European companies. The difference is in part owing to price controls

in 2012, which jumps from a slow-growing $8.3 billion to a more briskly growing $15.5 billion. Moreover, Wyeth's specialty business consists primarily of biologic products such as etanercept (Enbrel), whereas Pfizer's at present consists almost entirely of small molecules — most notably, pregabalin (Lyrica), which is predicted to have sales of $4.2 billion in 2012. We anticipate that large pharmaceutical companies will continue with such efforts to move their portfolios away from the unsustainable cost and risk of primary-care products and towards higher-priced specialty products with larger profit margins.

MG e farmaci innovativi



MG e farmaci innovativi

Se non si verifica alcun cambiamento, in assenza pertanto di interventi culturali ed organizzativi, l'evoluzione più probabile della MG sembrerebbe verso un ruolo di medicina del *bisogno soddisfatto* attraverso tecnologie sanitarie di costo contenuto (farmaco generico, consigli ed educazione sanitaria).

La gestione del *bisogno residuale*, ovvero la gestione del paziente "*non-responder*" (asma resistente alla terapia, ipertensione arteriosa refrattaria etc) verrebbe invece affidata alla medicina specialista, che utilizza per tale fine tecnologie innovative a costo elevato, quali farmaci innovativi (biologici e chimici), vaccini terapeutici, test genetici predittivi di malattia e test farmacogenetici.

La gestione del *bisogno assoluto* (soprattutto malattie rare e malattie orfane di terapia), come già oggi, continuerebbe ad essere gestita da un numero limitato di centri ad elevata specializzazione.

MG e farmaci innovativi

In una fase di rapida ed importante evoluzione della scienza, della tecnologia e di conseguenza della assistenza, diviene necessario per la Medicina Generale la definizione del proprio ruolo con riferimento alla produzione di conoscenza (la Scienza) ed all’utilizzo delle tecnologie (la Tecnologia).

MG e farmaci innovativi

Il ruolo della MG nella produzione di nuova conoscenza comporta una analisi più generale sul rapporto tra Medicina e Ricerca

•***Ricerca Primaria***

La ricerca primaria è rappresentata dalla produzione di dati ed informazioni direttamente dalle fonti primarie, attraverso metodi sperimentali o osservazionali, rappresenta ancora oggi la base principale per la decisione clinica.
La ricerca primaria in Medicina Generale in Italia avviata nel 2001, è stata limitata da una normativa limitata negli aspetti di incentivazione prevista per la medicina specialistica ed ospedaliera e le esperienze sono state sostanzialmente limitate
Oggi i nuovi farmaci destinati alla Medicina Generale sono in assoluto assai meno del decennio scorso e la quantità di ricerca clinica condotta in Italia in ambito di Cure Primarie risulta in assoluto ridotta.

MG e farmaci innovativi

Ricerca Secondaria

La ricerca secondaria è rappresentata dalla aggregazione di ricerche primarie, nella forma di revisione di esperti, di revisioni sistematiche, di metanalisi, di conferenze di consenso oppure di HTA.

Attraverso tale aggregazione di studi primari viene prodotto un nuovo livello di conoscenza rispetto alle fonti utilizzate. E' usata in modo sempre maggiore per il processo decisionale, sia in ambito clinico sul singolo paziente che in ambito sanitario su popolazioni aggregate di pazienti e rappresenta la base della medicina e della assistenza basate sulle prove di efficacia.

MG e farmaci innovativi

- **Ricerca Terziaria**

La ricerca terziaria è rappresentata dalla valuta dell'impatto delle decisioni basate sui risultati della ricerca primaria e secondaria nei confronti degli esiti clinici, economici ed umanistici in una popolazione.

E' probabile che il ruolo della Medicina Generale sia rilevante nella ricerca terziaria e marginale nella ricerca primaria.

MG e farmaci innovativi

22 Novembre 2008: La sfida dei medici di famiglia, ""al via il primo osservatorio per i farmaci innovativi""

Cricelli: "Senza il nostro impegno l'intero sistema non può reggere"

Firenze, 22 novembre 2008 – "Nasce il primo osservatorio per lo studio dei farmaci innovativi. È una sfida, ma senza il nostro impegno il rischio reale è che l'intero sistema del farmaco 'salti'. Sono convinto che i medici di medicina generale abbiano l'intelligenza e la creatività per farsi carico di questa sfida e vincerla". Con queste parole Claudio Cricelli, presidente della Società Italiana di Medicina Generale (SIMG), a chiusura del 25° Congresso Nazionale della Società in corso a Firenze, presenta la proposta innovativa per far fronte alla difficile situazione economica. L'osservatorio avrà l'obiettivo di dar vita a un nuovo rapporto tra medicina generale e farmaci innovativi che oggi rispondono a una logica esclusivamente specialistica. "È necessario chiedersi se il modello su cui è stato finora impostato il sistema del farmaco possa reggere. Il ruolo della medicina generale in questi anni è stato decisivo. Ma nel 2015 avremo solo farmaci generici e farmaci costosi. Il mondo cambierà in modo significativo". La nascita dell'osservatorio per lo studio dei farmaci innovativi, che avrà sede a Firenze, risponde allo scenario che si sta delineando: malattie croniche, come diabete e ipertensione, assorbiranno poche risorse per trattare il singolo individuo. Invece altre malattie, come quelle oncologiche, richiederanno grandi risorse. "È una situazione con risvolti paradossali: curare il paziente diabetico costerà meno rispetto alle cifre richieste per un malato oncologico – continua Cricelli". Non solo. "Nei prossimi anni – conclude Cricelli – dovremo lavorare a costi decrescenti, a salario invariato, ma con un necessario aumento di produttività del 25%. Di qui la sfida

"…Ma nel 2015 avremo solo farmaci generici e farmaci costosi …"

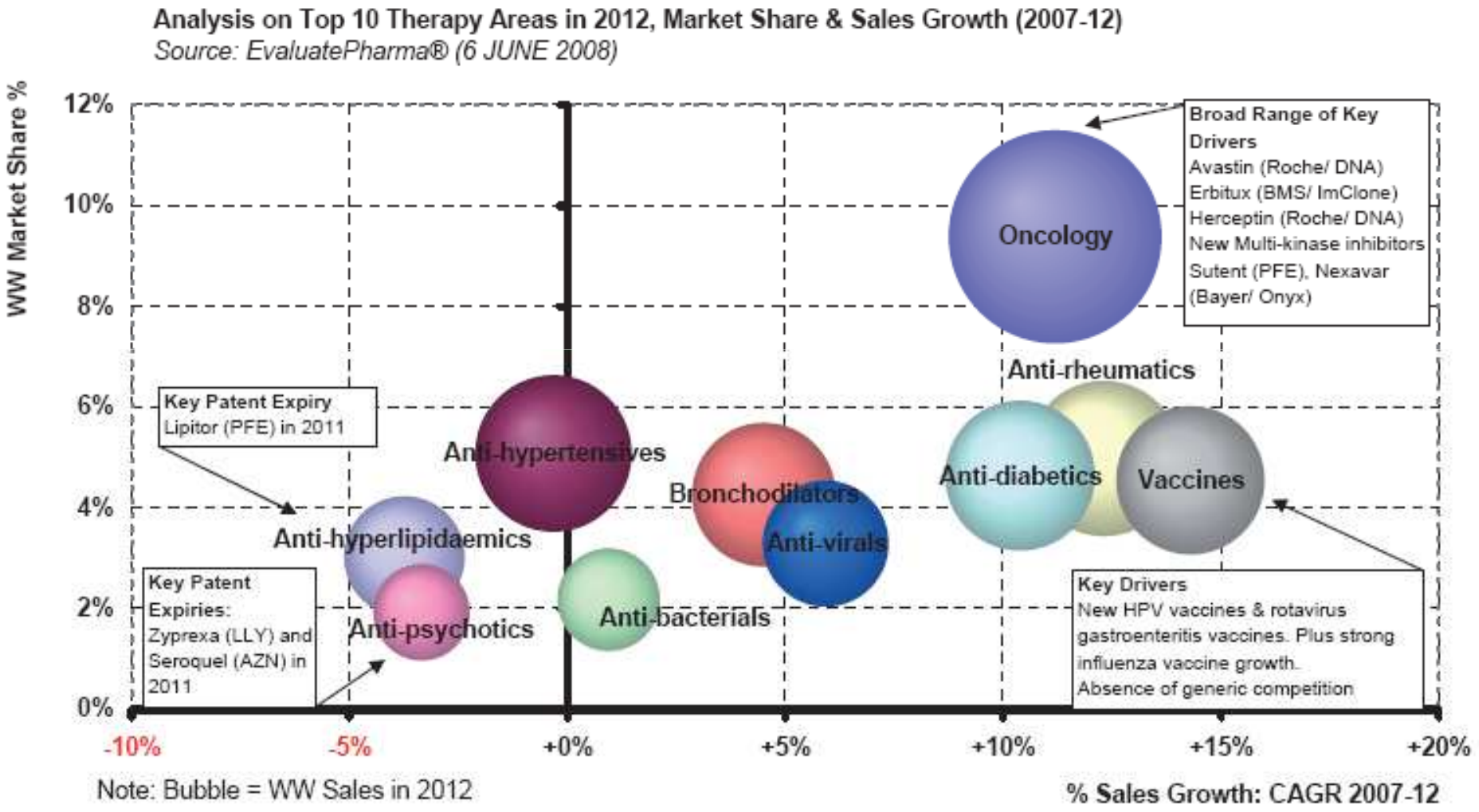
MG e farmaci innovativi

Che cosa fare da subito?

- Tenere conto dei sistemi di HTA sviluppati della MG e promuoverne la crescita a livello nazionale
- Inserire la MG nei sistemi regolatori
- Promuovere (da parte di tutti) la ricerca in MG
- Partecipare alla discussione sulla innovazione terapeutica

  Partecipare alla definizione delle linee guida sul trasferimento dei test genetici nella pratica medica

Aree Terapeutiche nel 2012



World Preview 2012