II REUNIÓN EN ENFERMEDADES AUTOINMUNES Y SISTÉMICAS. Bilbao, 25 y 26 de junio de 2009

Industria farmacéutica e investigación clínica:

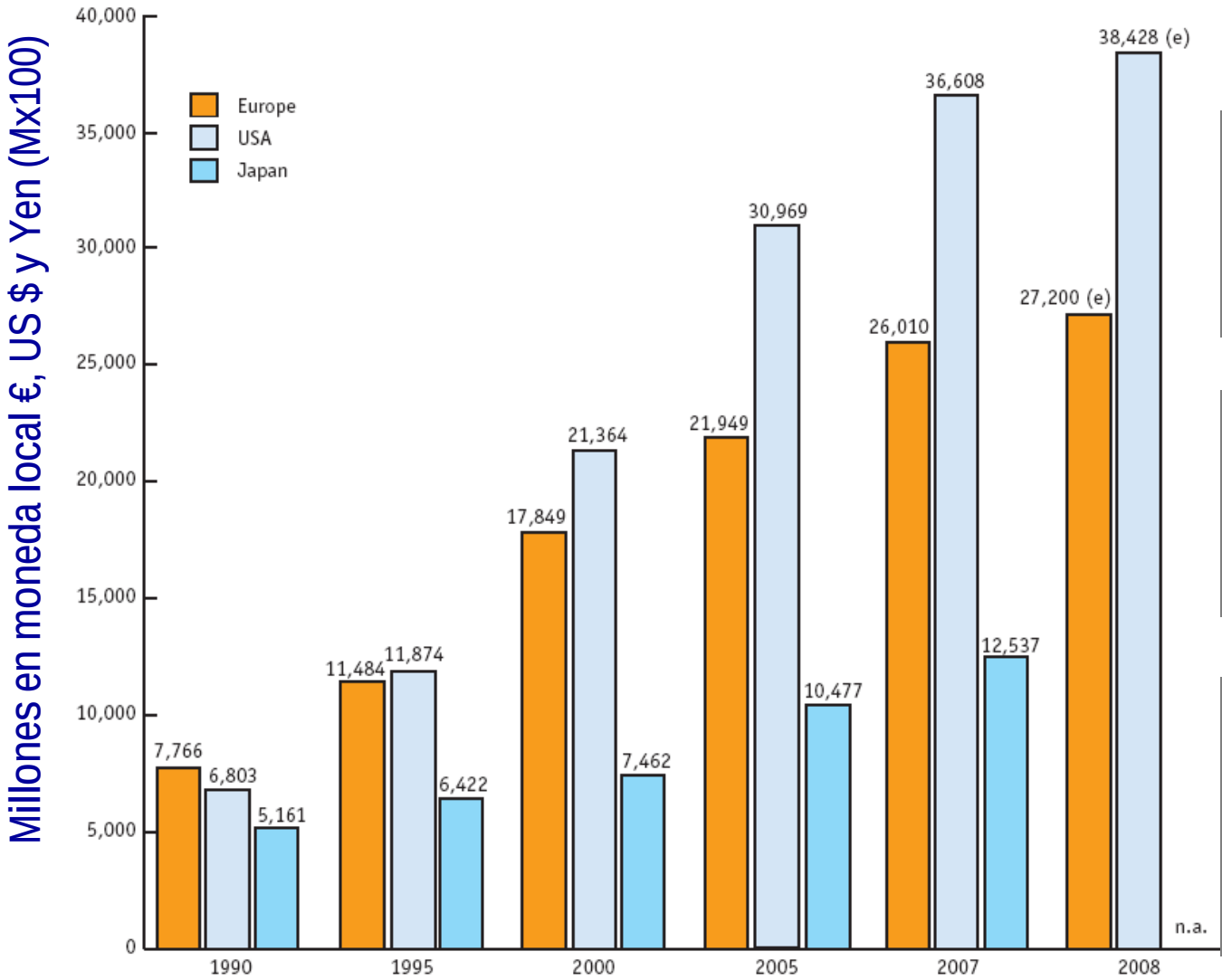
¿Una colaboración necesaria?

Martín Ballarín Milán
Director Científico de Laboratorios Menarini S.A

Índice de la sesión

- **Datos de inversión en I+D farmacéutica.**
- **Una colaboración necesaria: Definición de conflicto de intereses.**
- **Problemas más frecuentes y posibles explicaciones:**
  - ✓ **¿La industria presiona a las agencias reguladoras?.**
  - ✓ **¿Se cierran precozmente los estudios?**
  - ✓ **¿Hay sesgos en la selección de los pacientes?**
  - ✓ **¿Son de mala calidad los estudios?**
  - ✓ **¿Los estudios favorecen sus intereses?**
  - ✓ **¿Investiga en enfermedades que no existen?**

Inversión en I+D farmacéutica en Europa, EEUU y Japón (1990-2007)



Inversión en I+D

EEUU: ⬆ 5,6

Europa: ⬆ 3,5

Mercado 2007

EEUU: 45,9 %

Europa: 31,1 %

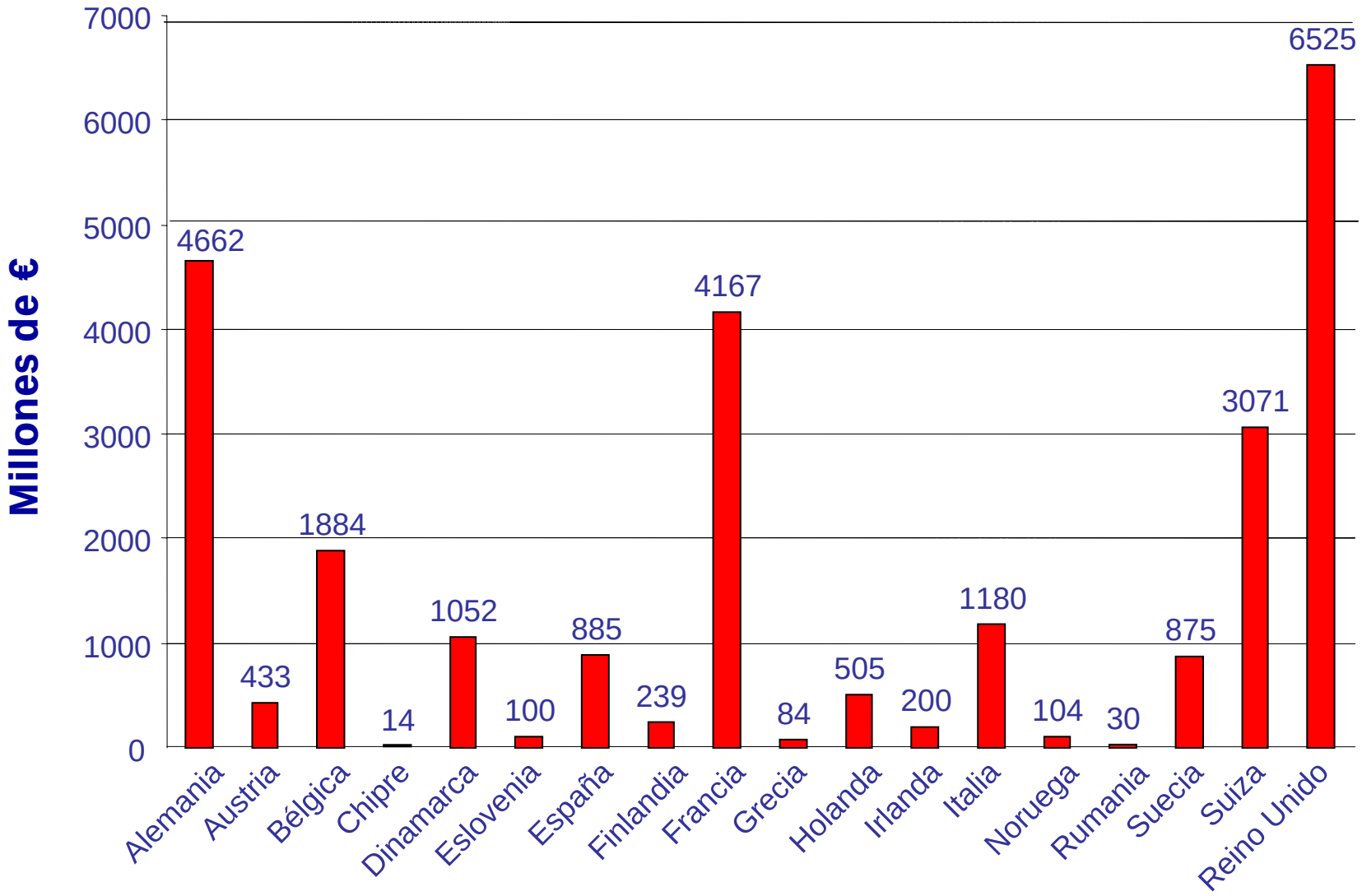
Nuevas moléculas 2004 - 2008

EEUU: 66 %

Europa: 26 %

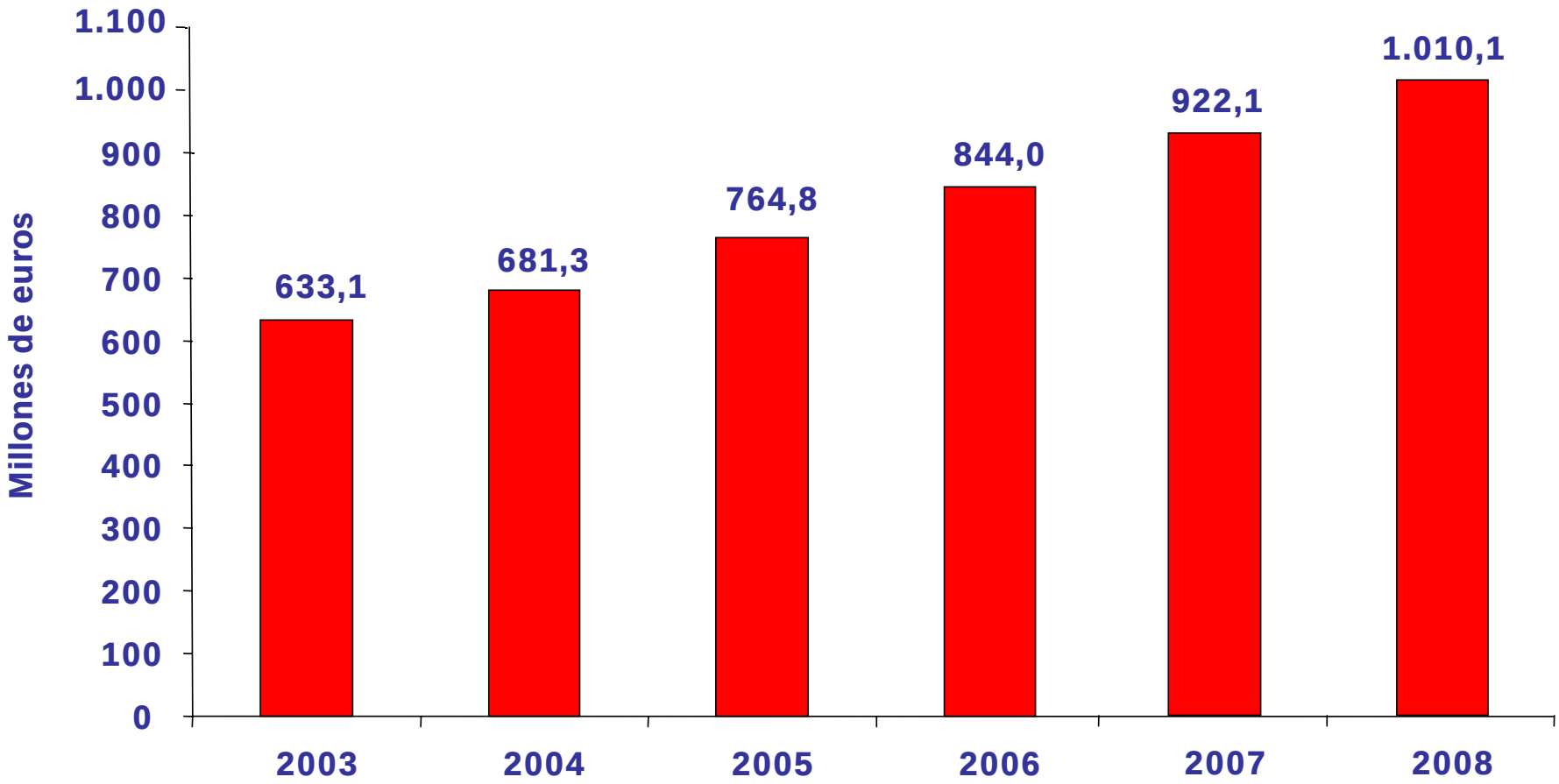
Fuente: EFPIA member associations, PhRMA, JPMA

Inversión de I+D farmacéutica en Europa 26.010 millones de €



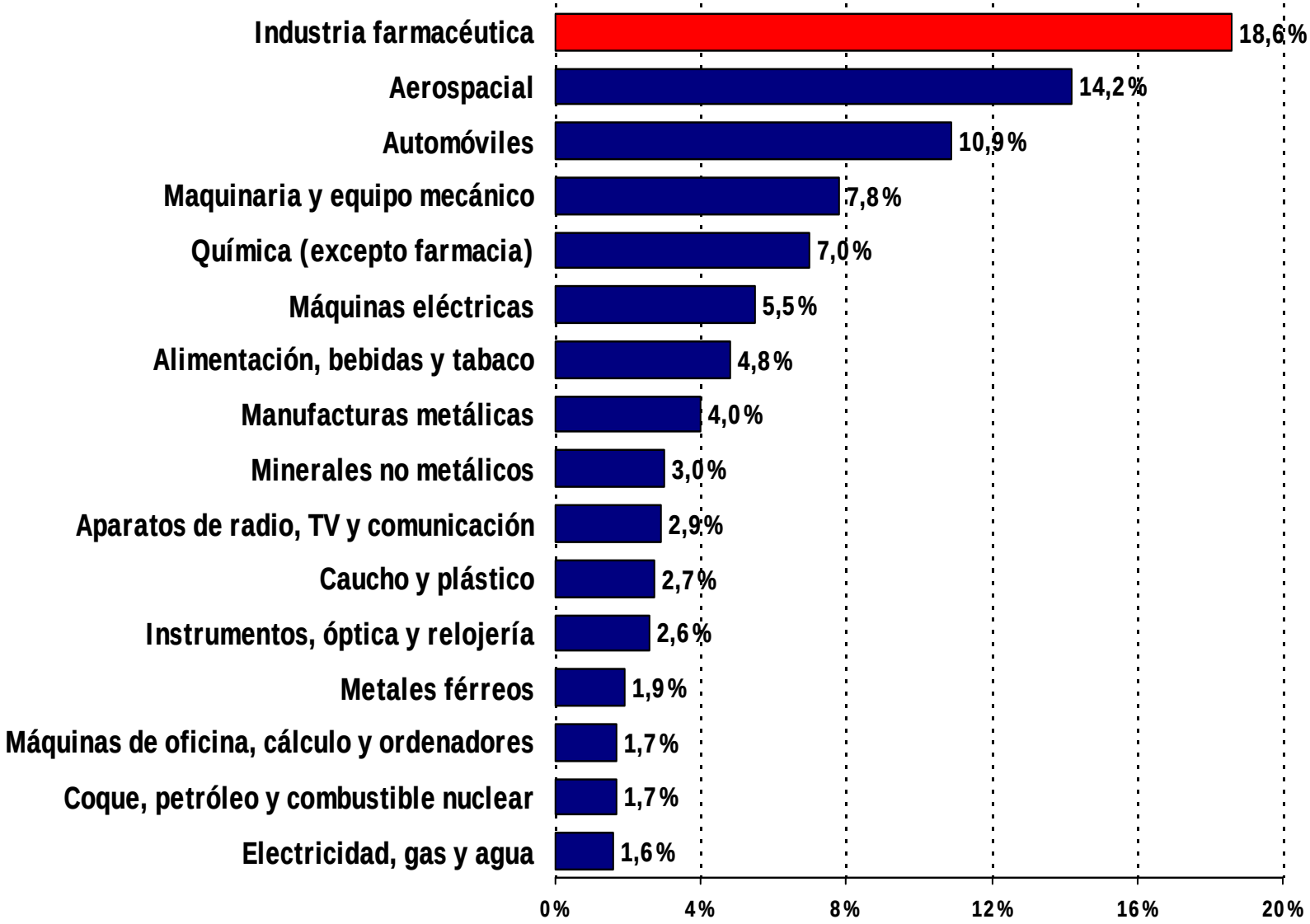
Fuente: EFPIA members association (datos de 2006 principalmente)

Inversión en I+D farmacéutica en España (valor)



Fuente: INE. Estadística de I+D. Varios años y encuesta 2008.

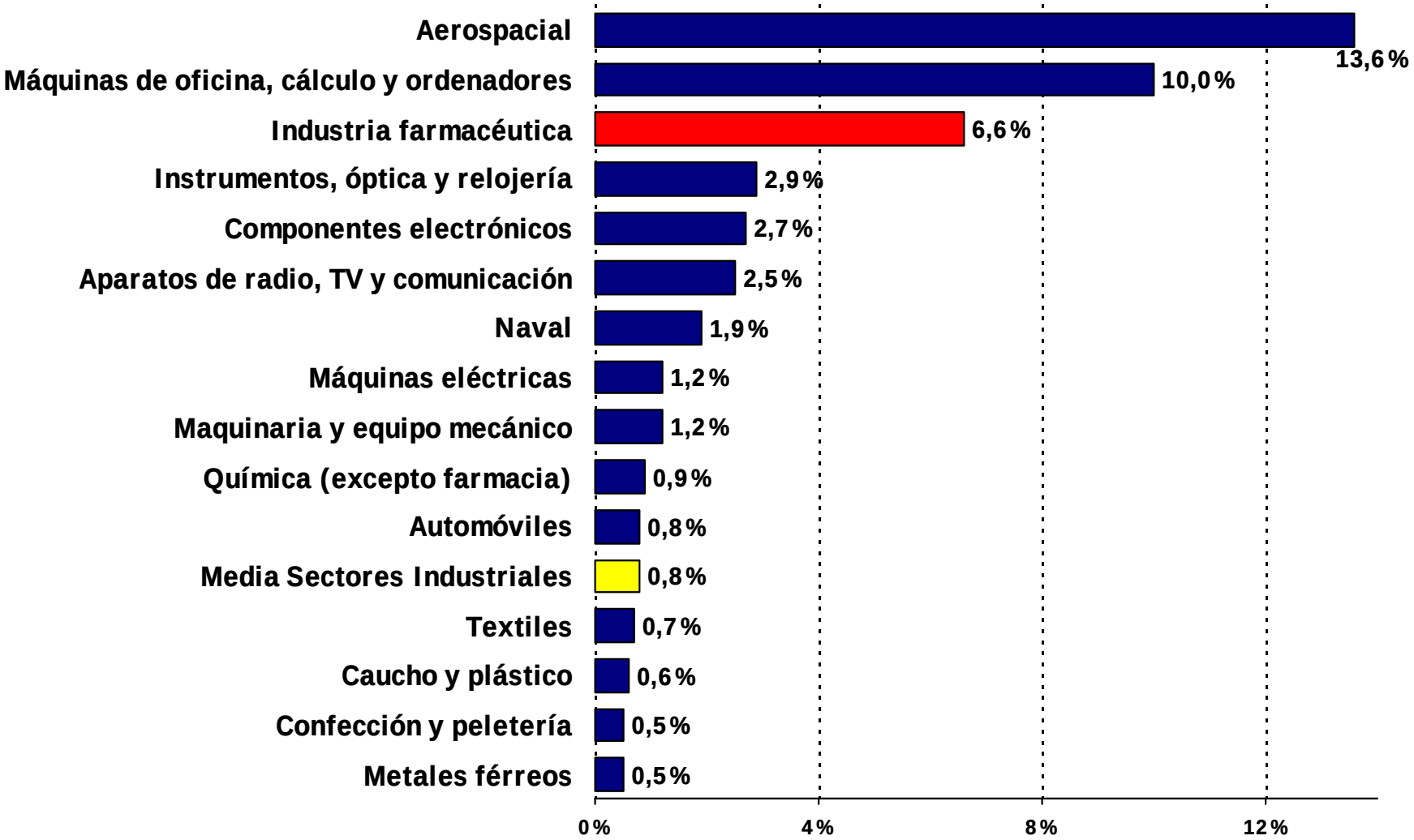
Inversión en I+D por sectores industriales en España (2006)



Fuente: INE. Encuesta sobre Innovación Tecnológica en las Empresas. 2006.

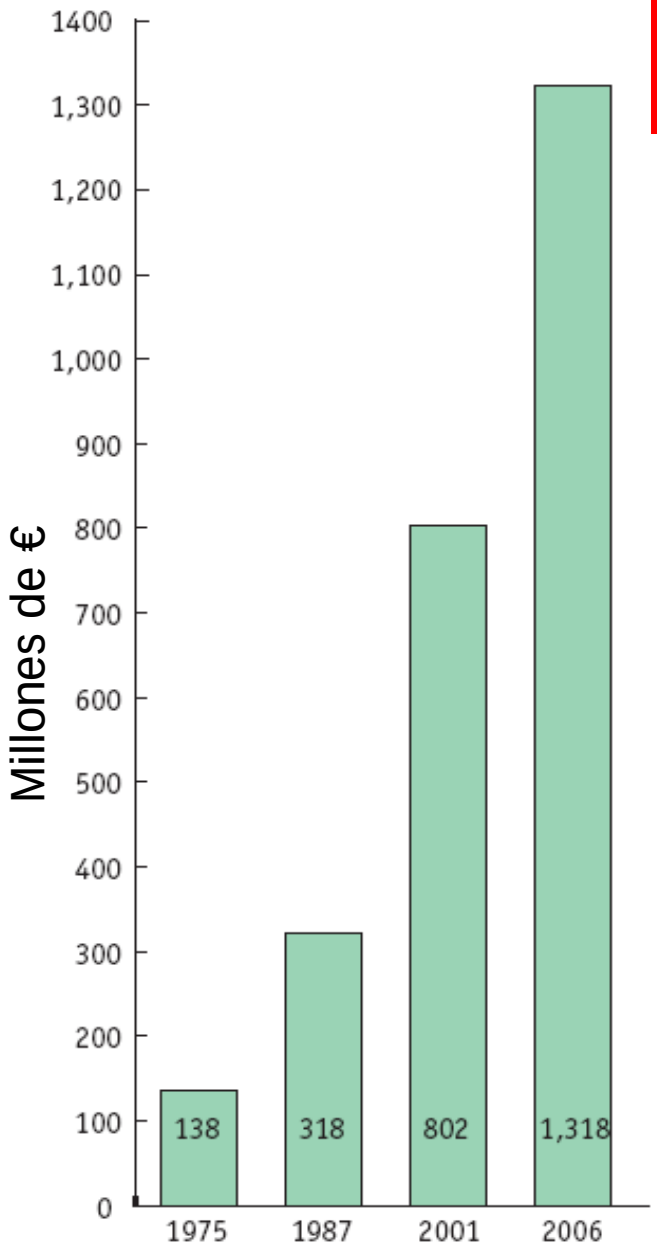
Inversión en I+D por sectores industriales en España (2006)

Inversión en I+D de cada sector como % de sus ingresos totales España.



Fuente: INE. Encuesta sobre Innovación Tecnológica en las Empresas. 2006.

Evolución del coste de una NEQ o una NEB de la I+D farmacéutica



La I+D farmacéutica es:

- **Larga:** Cada Nueva Entidad Química (NEQ) tarda entre 12 y 13 años desde que se sintetiza por primera vez hasta que llega al mercado.

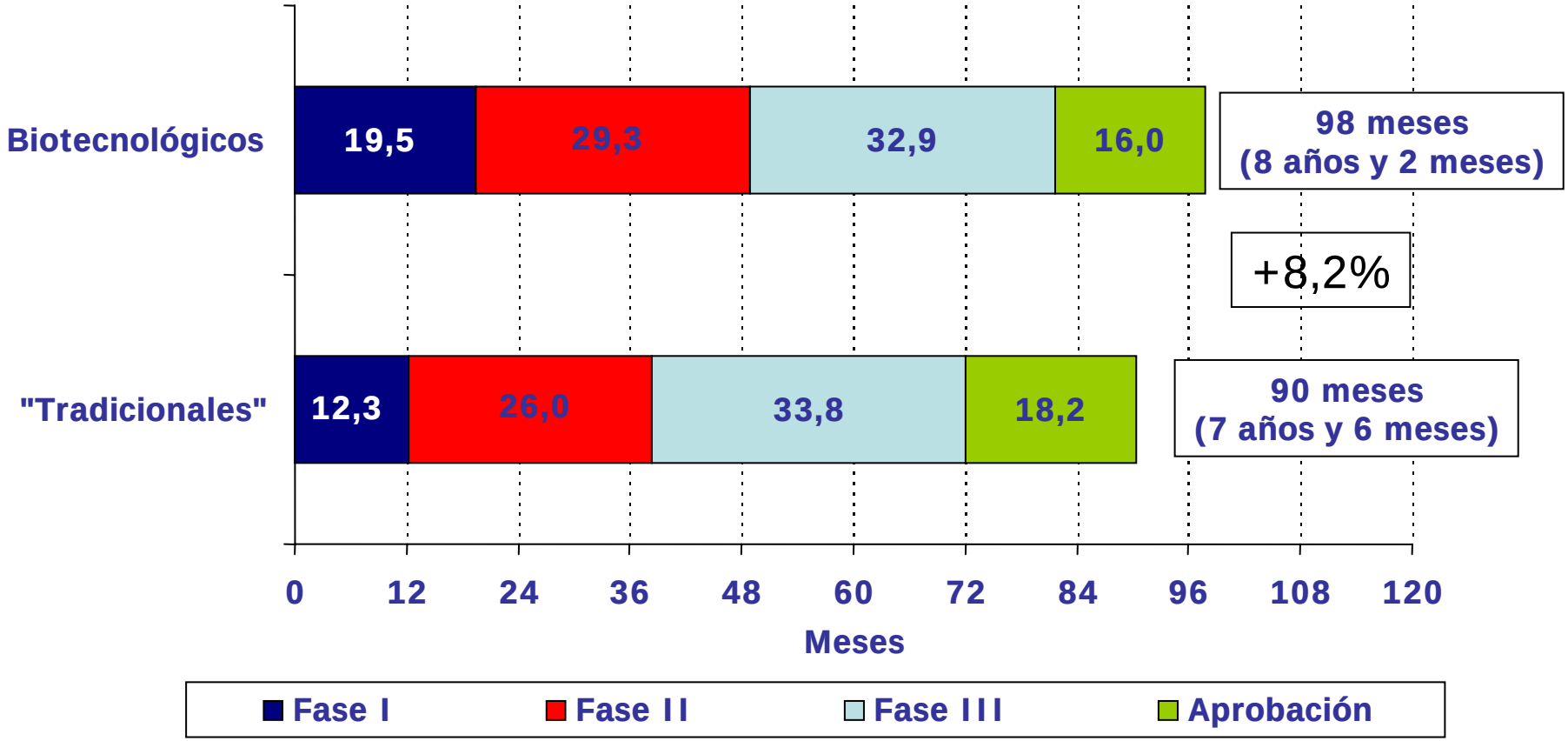
- **Costosa:** La inversión media por NEQ en I+D es de 1.059 millones de €.

- **Arriesgada:** Sólo 1 ó 2 NEQ entre 10.000 sustancias superan todo el proceso de I+D y se convierten en medicamentos.

DiMasi JA. Tufts University, Centre of Study of Drug Development, 2007.

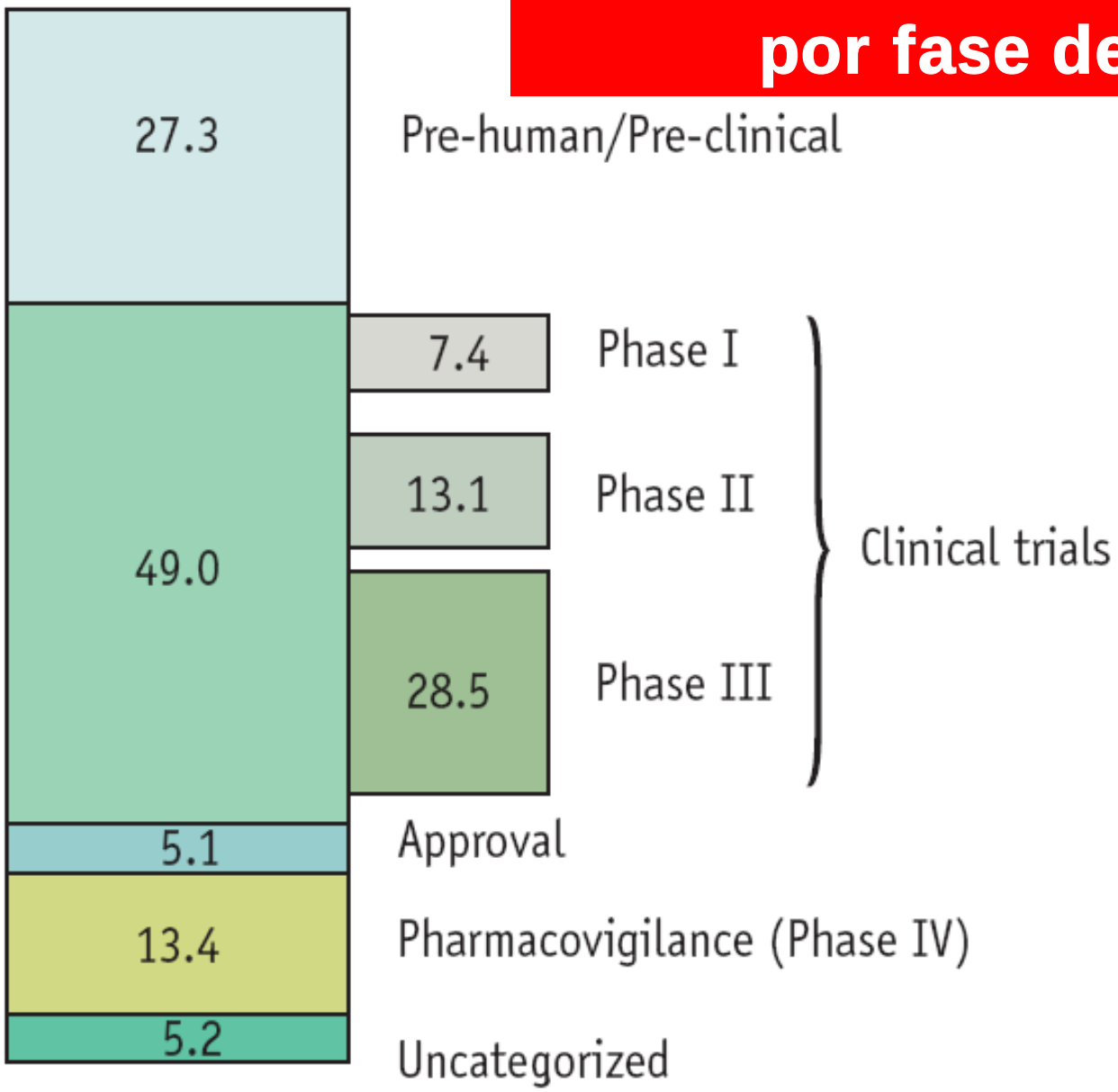
Plazos de la I+D clínica de los biotecnológicos y tradicionales

Plazos de desarrollo clínico y aprobación



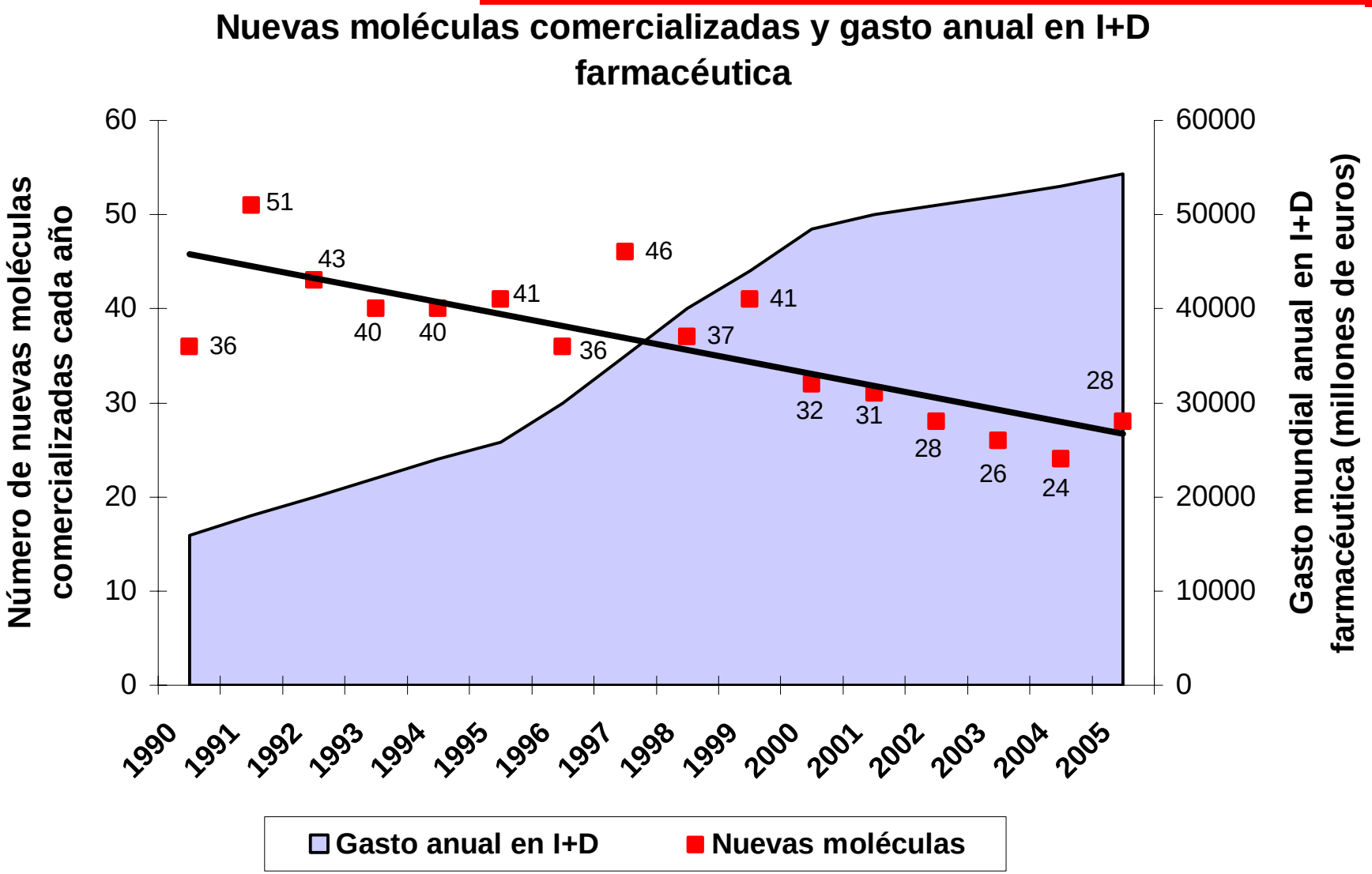
DiMasi JA, Grabowski HG. "The cost of biopharmaceutical R&D: Is biotech different?" Managerial and decision economics 2007; 28: 469-479.

Costes de la I+D farmaceútica por fase de investigación



Fuente: PhRMA, Annual Membership Survey 2009 (% calculados de datos 2007)

La productividad de la I+D farmacéutica es decreciente

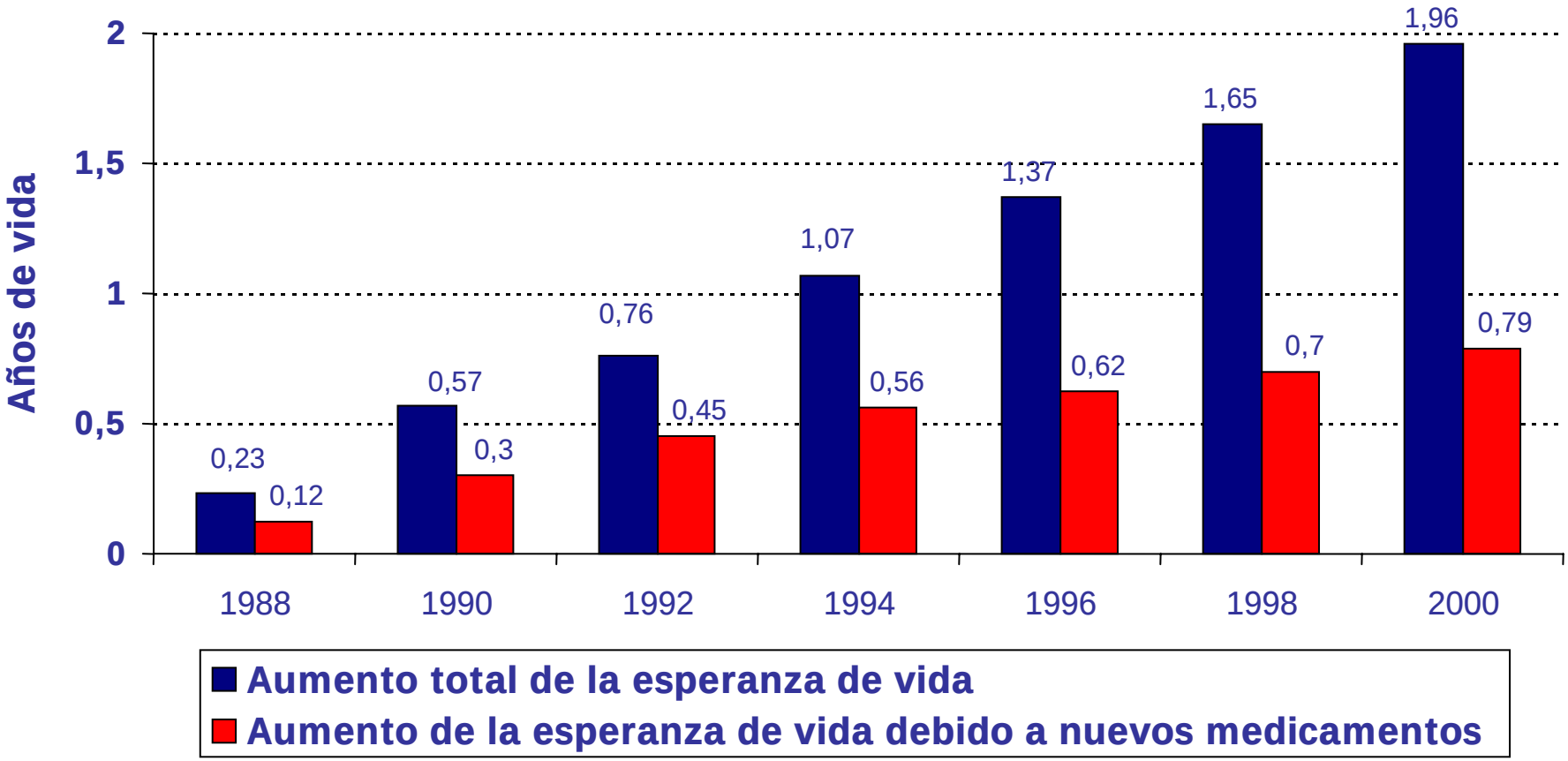


Fuente: EFPIA citando a CMR international y datos de las asociaciones de IF

Resultados de la I+D farmaceútica

El 90% de los medicamentos ha sido desarrollado por la industria farmacéutica

Aumento de la esperanza de vida



Lichtenberg FR, "The impact of new drug launches on longevity: evidence from longitudinal disease-level data from 52 countries, 1982-2001", NBER, June 2003

Conflicto de intereses: ¿Quiénes están implicados?

	INTERESES PRIMARIOS	INTERESES SECUNDARIOS
INDUSTRIA	REGISTRO: EN MENOR TIEMPO Y COSTE	AMORTIZAR LA INVERSIÓN OBTENER BENEFICIOS
MÉDICO	SALUD DEL PACIENTE INTEGRIDAD DE LA I+D	PROMOCIÓN PROFESIONAL COMPENSACIÓN ECONÓMICA
PACIENTE	CURACIÓN ENFERMEDAD MEJOR ATENCIÓN SANITARIA	BENEFICIO COMUNITARIO MEJORA TERAPÉUTICA
INSTITUCIÓN	MINIMIZAR GASTOS RACIONALIZAR COSTES	PRESTIGIO DEL CENTRO COMPENSACIÓN ECONÓMICA

Bekelman JE. JAMA. 2003;289:454-465

¿La I+D farmacéutica influencia en las agencias reguladoras?

Making regulation responsive to commercial interests: streamlining drug industry watchdogs

John Abraham

Has the pharmaceutical industry skilfully managed to achieve an unhealthy influence over European drug regulatory agencies?

After the thalidomide disaster the public expected drug regulation would be independent of the interests of the pharmaceutical industry

In the past 15 years the regulatory agencies have been overly influenced by the industry's desire for rapid drug approvals

Regulatory agencies have become heavily dependent on industry fees for their survival

National agencies now find themselves competing with each other for industry fees for regulatory work

Abraham J, BMJ. 2002 16; 325(7373): 1164–1169

¿La I+D farmacéutica influencia en las agencias reguladoras?

En 1999 salieron al mercado de USA los dos primeros fármacos basados en el conceptos de la COX-2 selectividad, llamados coxibs (rofecoxib y celecoxib). El éxito en el mercado fue impresionante y vendieron a nivel mundial 2,5 billones de $ en 2003.

Algunos aspectos del proceso de registro fueron excepcionales. El ensayo clínico comparativo y aleatorizado básico para demostrar su menor efecto gastrolesivo fue publicado un año más tarde de obtener la aprobación para la comercialización.

¿La I+D farmacéutica influencia en las agencias reguladoras?

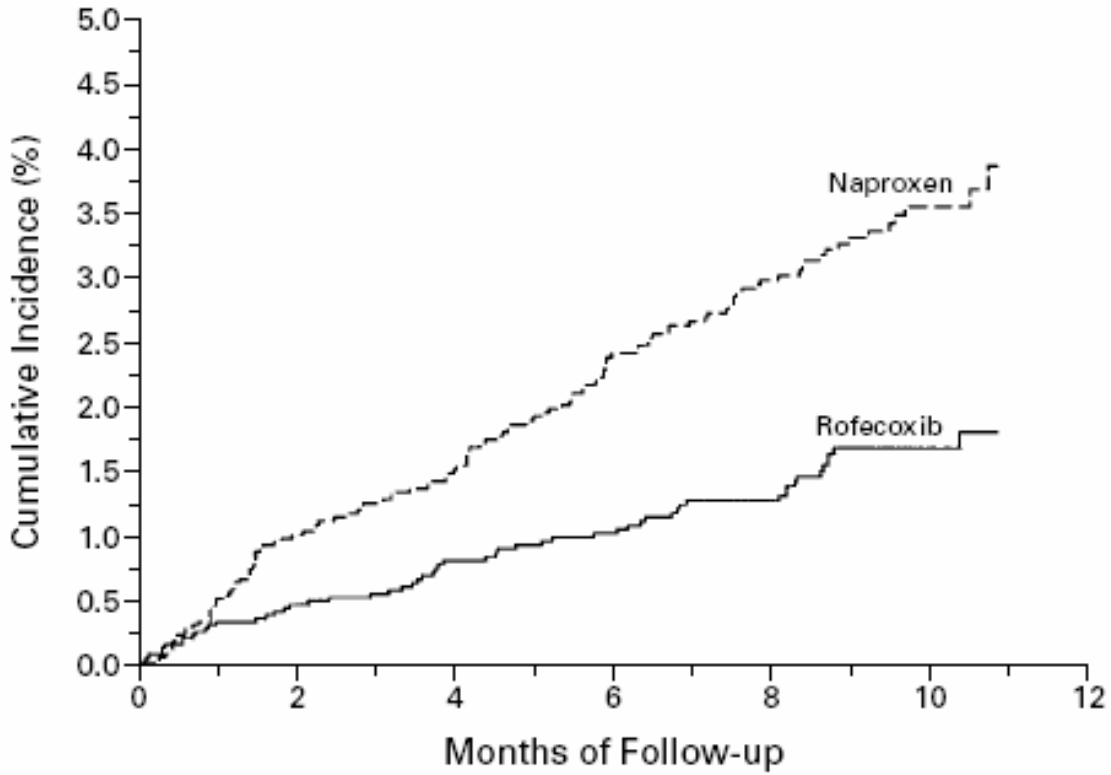
The New England Journal of Medicine

COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

CLAIRE BOMBARDIER, M.D., LOREN LAINE, M.D., ALISE REICIN, M.D., DEBORAH SHAPIRO, DR.P.H., RUBEN BURGOS-VARGAS, M.D., BARRY DAVIS, M.D., PH.D., RICHARD DAY, M.D., MARCOS BOSI FERRAZ, M.D., PH.D., CHRISTOPHER J. HAWKEY, M.D., MARC C. HOCHBERG, M.D., TORE K. KVIEN, M.D., AND THOMAS J. SCHNITZER, M.D., PH.D., FOR THE VIGOR STUDY GROUP

Bombardier C. N Engl J Med 2000;343:1520-1528

¿La I+D farmacéutica influencia en las agencias reguladoras?



No. at Risk

Rofecoxib	4047	3641	3402	3180	2806	1073	533
Naproxen	4029	3644	3389	3163	2796	1071	513

Figure 1. Cumulative Incidence of the Primary End Point of a Confirmed Upper Gastrointestinal among All Randomized Patients.

Supported by a grant from Merck.

Dr. Bombardier has received clinical research support from Aventis Pharma, Merck Research Laboratories, and Merck Frosst Canada. She has served as a consultant to Knoll Pharmaceutical, Aventis Canada, Schering Canada, Merck Research Laboratories, and Wyeth–Ayerst.

Dr. Laine has received clinical research support from Merck, Wyeth–Ayerst, and AstraZeneca. He has served as a consultant to Merck, Searle, Johnson & Johnson, AstraZeneca, Wyeth–Ayerst, and Tap Pharmaceuticals.

Dr. Burgos-Vargas has received clinical research support from Merck Sharp & Dohme, Pfizer, and Boehringer Ingelheim. He has served as a consultant to Merck and has been a member of a speakers' bureau sponsored by Merck Sharp & Dohme.

Dr. Davis has served as a consultant to Mirvant, Merck Research Laboratories, Parke-Davis, and SmithKline Beecham.

Dr. Day has received clinical research support from Merck, Searle, Pfizer, Roche, and Amgen. He has served as a consultant to Merck, Searle, and Pfizer. He has been a member of speakers' bureaus sponsored by Merck Sharp & Dohme, Searle, Pfizer, and SmithKline Beecham.

Dr. Ferraz has received clinical research support from Bristol-Myers Squibb, Merck Sharp & Dohme, and Aventis Pharma. He has served as a consultant to Aventis Pharma.

Dr. Hawkey has received clinical research support from AstraZeneca, Asta Medica, Boehringer Ingelheim, Boots Healthcare International, Cell Tech, Eisai, Elan, Merck Research Laboratories, NicOx, and Novartis. He has served as a consultant to AstraZeneca, Abbott, Cell Tech, Eisai, Merck Research Laboratories, NicOx, Novartis, Parke-Davis, and Synthelabo Pharmacie. He has been a member of speakers' bureaus sponsored by AstraZeneca, Boehringer Ingelheim, Boots Healthcare International, Takeda, Wyeth Lederle, and Merck Research Laboratories.

Dr. Hochberg has received clinical research support from Merck and Quintiles (Aventis Pharma). He has served as a consultant to Aventis Pharma, Biomatrix, Merck, Negma Laboratories, Procter & Gamble, Roche, and Wyeth–Ayerst. He owns stock in Johnson & Johnson, Eli Lilly, Merck, Procter & Gamble, and Schering-Plough.

Dr. Kvien has received clinical research support from Merck, Searle, Aventis Pharma, and Schering-Plough. He has served as a consultant to Merck, Searle, Aventis Pharma, and Schering-Plough. He has been a member of a speakers' bureau sponsored by Merck and Aventis Pharma.

Dr. Schnitzer has received clinical research support from Abbott, Boehringer Ingelheim, Johnson & Johnson, McNeil Consumer Products, Merck, Novartis, Ortho-McNeil, Parke-Davis, Searle, and Wyeth–Ayerst. He has served as a consultant to Boehringer Ingelheim, Merck, Novartis, Ortho-McNeil, Searle, and SmithKline Beecham. He has been a member of speakers' bureaus sponsored by Boehringer Ingelheim, Merck, Ortho-McNeil, Wyeth–Ayerst, and Searle.

Dr. Weaver has received clinical research support from Merck, Searle, Immunex, Wyeth–Ayerst, Aventis Pharma, Pharmacia–Upjohn, Eli Lilly, Connetics, Parke-Davis, Procter & Gamble, Pfizer, Hoffmann–LaRoche, Centocor, Amgen, Cyprus Bioscience, Helsinn, Novartis, and Boehringer Ingelheim. He has served as a consultant to Merck, Searle, Immunex, Wyeth–Ayerst, Aventis Pharma, Pharmacia–Upjohn, Eli Lilly, Connetics, Parke-Davis, Procter & Gamble, Pfizer, Hoffmann–LaRoche, Centocor, Amgen, Cyprus Bioscience, Helsinn, Novartis, and Boehringer Ingelheim. He has been a member of speakers' bureaus sponsored by Merck, Searle, Immunex, Wyeth–Ayerst, Aventis Pharma, Pharmacia–Upjohn, Eli Lilly, Connetics, Parke-Davis, Procter & Gamble, Pfizer, Hoffmann–LaRoche, Centocor, Amgen, Cyprus Bioscience, Helsinn, Novartis, and Boehringer Ingelheim. He is on the board of directors of MGI Pharma.

Bombardier C. N Engl J Med 2000;343:1520-1528

¿La I+D farmacéutica influencia en las agencias reguladoras?

RESULTADOS MÁS RELEVANTES DEL ESTUDIO

	% TOXICIDAD GI	% INFARTOS MIOCARDIO	↑ TAS mm Hg	↑ TAD mm Hg
ROFECOXIB	2,1*	0,4	4,6	1,7
NAPROXEN	4,5	0,1*	1,0*	0,1*

* p<0.05

Bombardier C. N Engl J Med 2000;343:1520-1528

¿La I+D farmacéutica influencia en las agencias reguladoras?

Learning the Value of Drugs — Is Rofecoxib a Regulatory Success Story?

Rebecca S. Eisenberg, J.D.

Controversy over recent revelations concerning the adverse cardiovascular effects of selective cyclooxygenase-2 (COX-2) inhibitors has generally been framed as a story of regulatory failure, in which the Food and Drug Administration (FDA) has failed in its mission to protect the public from unsafe products. But this simplistic understanding of the mission of the FDA seems to make failure all but inevitable, if the reliable observation of the risks and benefits of a drug requires rigorous long-term studies. Perhaps in an earlier era the goal of drug regulation was simply to protect the public from poisons.[1] Today, drug regulation guides the development of information that turns poisons, used advisedly, into drugs. From this perspective, the growing knowledge of the complex effects of COX-2 inhibitors might be retold as a story of regulatory success.

Drugs are information-rich chemicals that in some respects resemble other information products. Although we rely primarily on pharmaceutical firms to supply this information, we have reason to worry that, in an unregulated market, these firms would provide either too little information or distorted information. Getting profit-seeking companies to provide reliable information about the effects of drugs in patients is thus a major challenge for regulators.

Eisemberg RS. N Engl J Med 2005;352:1385-1386

¿Se cierran precozmente los estudios para mejorar los datos?

JAMA®

Randomized Trials Stopped Early for Benefit: A Systematic Review

Victor M. Montori; P. J. Devereaux; Neill K. J. Adhikari; et al.

Table 1. Characteristics of Randomized Clinical Trials (RCTs) Stopped Early for Benefit (N = 143)

Characteristic	No./Total (%)	
	RCTs Stopped Early/ RCTs Indexed in MEDLINE	RCTs Stopped Early/ RCTs in Top-Impact Journals
Year of publication		
1975-1979	1/6574 (0.01)	0/620 (0)
1980-1984	1/12 653 (0.008)	1/1175 (0.1)
1985-1989	10/21 807 (0.05)	9/1938 (0.5)
1990-1994	19/38 712 (0.05)	15/3106 (0.5)
1995-1999	41/52 060 (0.08)	35/3594 (1.0)
2000-2004	71/58 537 (0.1)	47/3859 (1.2)
Area of study		
Cardiology	36 (25)	
Cancer (hematology-oncology)	30 (21)	
HIV/AIDS	17 (12)	
Critical care	10 (7)	
Other areas	50 (35)	

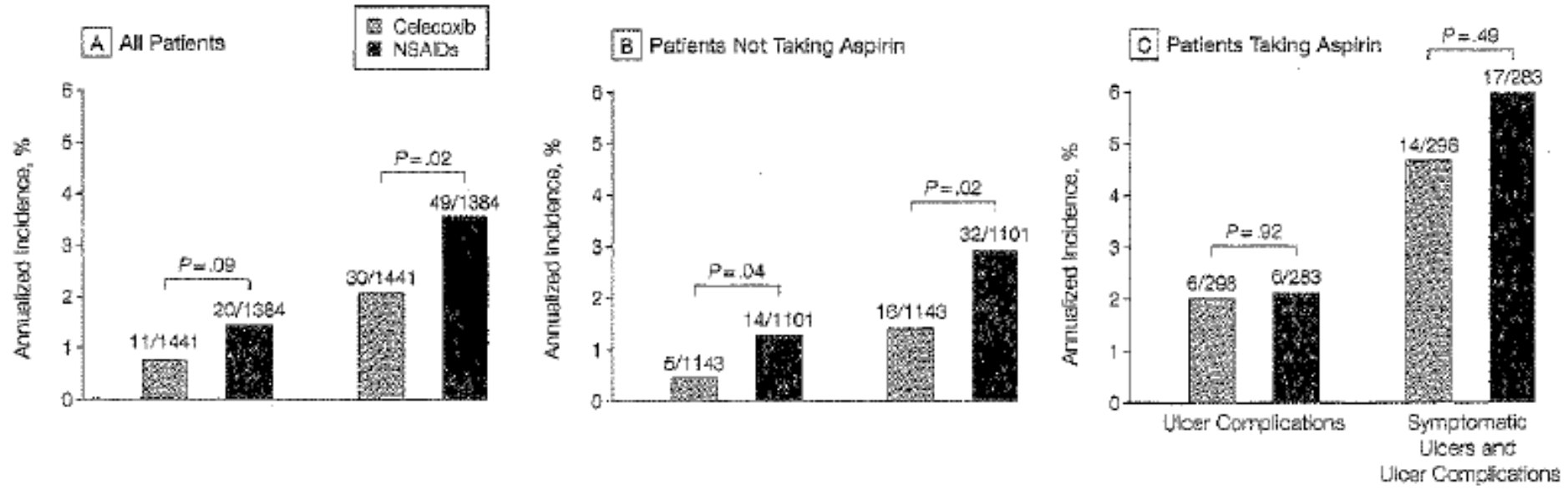
Montori VM. JAMA 2005;294(17):2203-2209

¿Se cierran precozmente los estudios para mejorar los datos?

ORIGINAL CONTRIBUTION JAMA-EXPRESS

Gastrointestinal Toxicity With Celecoxib vs Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis

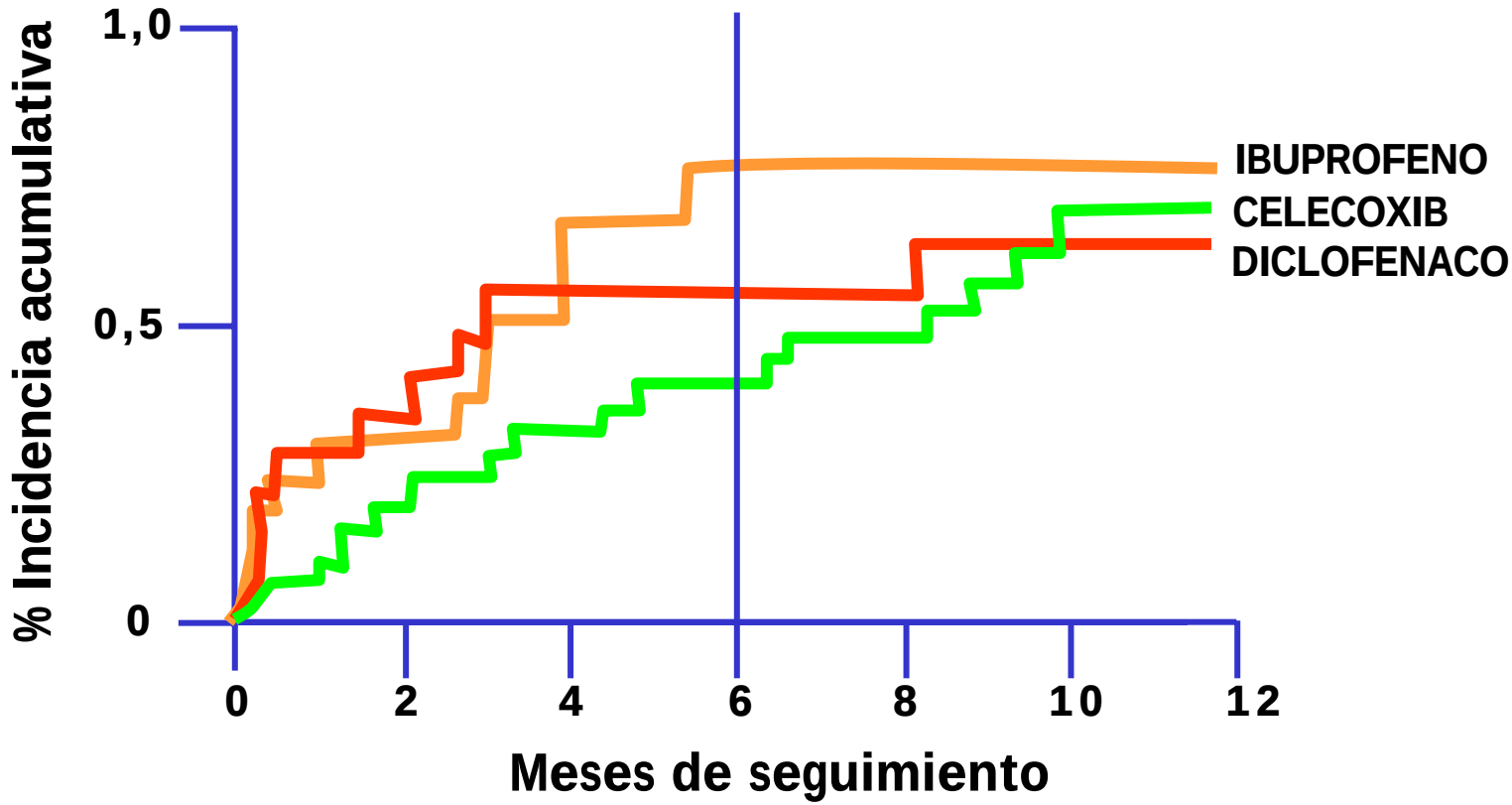
The CLASS Study: A Randomized Controlled Trial



Silverstein FE. JAMA 2000;284(10):1247-1255

¿Se cierran precozmente los estudios para mejorar los datos?

RESULTADOS DE CELECOXIB A 12 MESES EN EL ESTUDIO CLASS

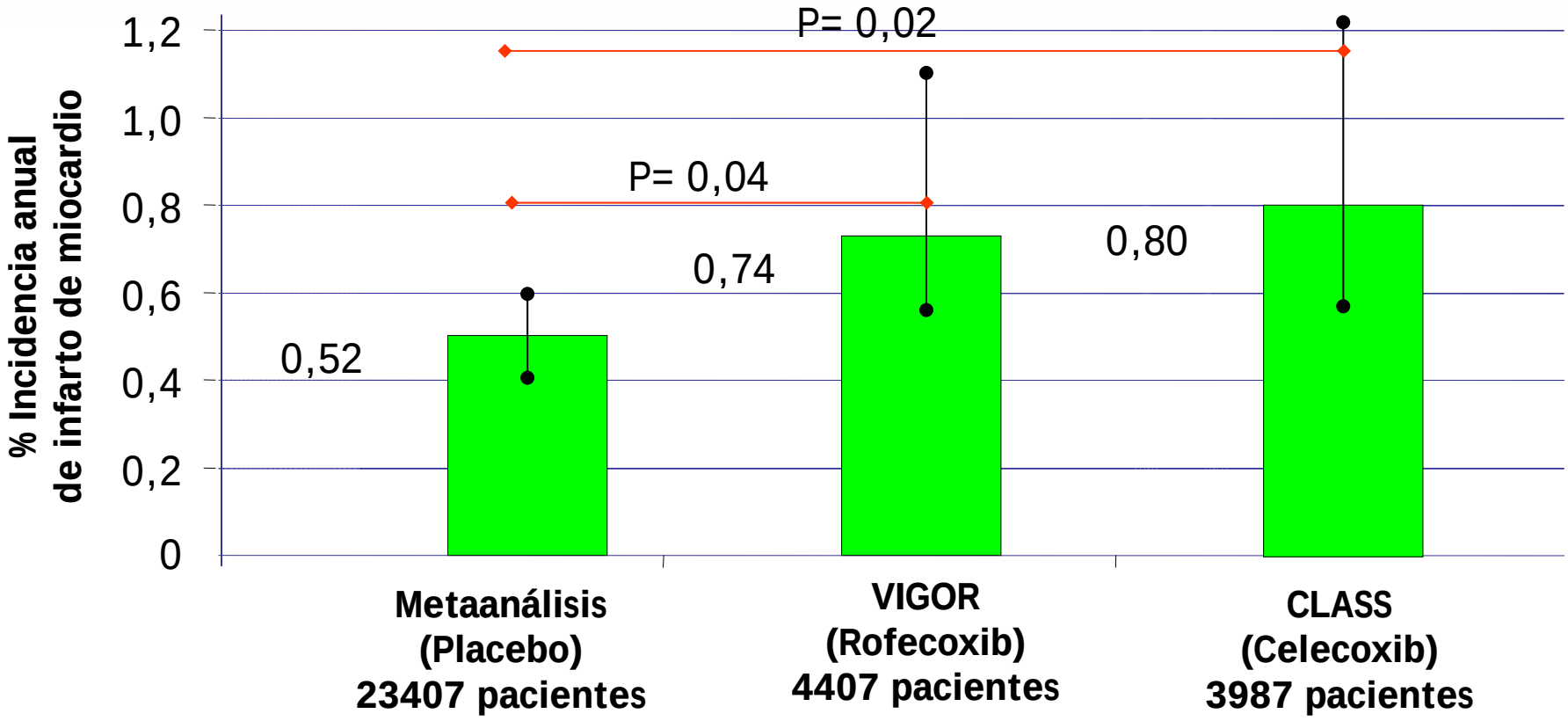


Lu HL. Statistical reviewer briefing document for the Advisory Comitee. June 14, 2000.
http://www.fda.gov/cder/foi/nda/2002/20-998S009_Celebrex_start.pdf

¿Se cierran precozmente los estudios para mejorar los datos?

Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs?

Adequate analysis of the CLASS trial indicates that this may not be the case



Mukherjee D. JAMA 2001; 286: 954-959

¿Hay sesgos en la selección de los pacientes para mejorar resultados?

TABLE 2. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ROFECOXIB GROUP (N=4047)	NAPROXEN GROUP (N=4029)
Age — yr	58±9	58±10
Female sex — no. (%)	3223 (79.6)	3215 (79.8)
Race or ethnic group — no. (%)		
White	2761 (68.2)	2750 (68.3)
Black	207 (5.1)	202 (5.0)
Asian	101 (2.5)	85 (2.1)
Hispanic	501 (12.4)	516 (12.8)
Other	477 (11.8)	476 (11.8)
Duration of disease — no. (%)		
Unknown	3 (0.1)	6 (0.1)
<2 yr	430 (10.6)	455 (11.3)
2–10 yr	1991 (49.2)	1996 (49.5)
>10 yr	1623 (40.1)	1572 (39.0)
Positive test for rheumatoid factor — no. (%)	2946 (72.8)	2967 (73.6)
Prior use of NSAIDs — no. (%)	3321 (82.1)	3331 (82.7)
Treatment for rheumatoid arthritis — no. (%)		
Glucocorticoids	2260 (55.8)	2263 (56.2)
Methotrexate	2263 (55.9)	2269 (56.3)
Other disease-modifying drugs	1847 (45.6)	1826 (45.3)
Low-dose H_2-receptor antagonists — no. (%)†	365 (9.0)	335 (8.3)
History of clinical gastrointestinal events	314 (7.7)	316 (7.8)
Global Disease Activity score‡		
Patient's assessment	2.0±0.9	2.0±0.9
Investigator's assessment	1.9±0.8	1.9±0.8

Table 2. Baseline Patient Characteristics*

Characteristics	Celecoxib Group (n = 3987)	NSAID Group (n = 3981)
Age, mean (range), y	60.6 (20-89)	59.8 (18-90)
>65 y, %	39.1	37.3
>75 y, %	12.2	11.4
Women, %	68.5	69.1
Race/ethnicity, %		
White	88.5	87.9
Black	7.5	8.2
Hispanic	2.7	2.8
Asian	0.7	0.8
Other	0.6	0.6
Primary rheumatoid arthritis, %	27.3	27.5
Duration of disease, mean (SD), y		
Osteoarthritis	10.3 (9.7)	10.1 (9.9)
Rheumatoid arthritis	11.3 (9.9)	10.7 (9.6)
NSAID therapy at study entry, %	81.4	81.6
Ibuprofen	21.7	20.9
Diclofenac	13.6	14.0
Potential risk factor, %		
History of gastrointestinal bleeding	1.7	1.5
History of gastrointestinal ulcer	8.4	8.1
Helicobacter pylori infection, %	38.5	38.2
Tobacco use, %	15.8	14.9
Alcohol use, %	30.9	30.1
Concurrent medications, %		
Aspirin (≤325 mg/d)	20.9	20.4
Corticosteroids	30.6	29.5
Anticoagulants	1.1	1.1

Bombardier C. N Engl J Med 2000;343:1520-1528
Silverstein FE. JAMA 2000;284(10):1247-1255

¿Hay sesgos en la selección de los pacientes para mejorar resultados?

	Non-user (n=202 916)	Ibuprofen (n=59 007)	Naproxen (n=70 384)	Celecoxib (n=22 337)	Rofecoxib ≤25 mg (n=20 245)	Rofecoxib >25 mg (n=3887)
Age (mean, SD) (years)	61·8 (9·0)	60·4 (8·1)	60·4 (8·1)	63·7 (8·9)	63·2 (8·8)	60·6 (8·1)
Women	127 458 (63%)	40 661 (69%)	48 592 (69%)	16 280 (73%)	14 830 (73%)	2552 (66%)
White	151 568 (75%)	40 065 (68%)	49 626 (71%)	16 246 (73%)	15 561 (77%)	2998 (77%)
TennCare enrolment, uninsured†	74 718 (37%)	18 247 (31%)	23 054 (33%)	5780 (26%)	5884 (29%)	1184 (31%)
Treatment for cardiovascular problems in past year‡	155 681 (77%)	49 684 (84%)	58 864 (84%)	19 778 (89%)	17 618 (87%)	3350 (86%)
Major cardiovascular disease§	69 150 (34%)	23 213 (39%)	27 011 (38%)	9625 (43%)	8507 (42%)	1640 (42%)
Cardiovascular drug¶	150 846 (74%)	48 183 (82%)	57 186 (81%)	19375 (87%)	17 243 (85%)	3256 (84%)
Treatment for musculoskeletal problems in past year‡						
NSAID use	0	39 620 (67%)	46 634 (66%)	16 630 (73%)	14 232 (70%)	2773 (71%)
Rheumatoid arthritis	2056 (1%)	1020 (2%)	1228 (2%)	1090 (5%)	519 (3%)	126 (3%)
Systemic lupus erythematosus	540 (0·3%)	206 (0·3%)	225 (0·3%)	200 (1%)	179 (1%)	25 (1%)
Other inflammatory arthropathy	353 (0·2%)	146 (0·2%)	166 (0·2%)	166 (1%)	106 (0·5%)	16 (0·4%)
Oral corticosteroids	32 594 (16%)	14 172 (24%)	17 190 (24%)	6978 (31%)	6013 (30%)	1282 (33%)
Methotrexate	1260 (1%)	513 (1%)	578 (1%)	563 (3%)	270 (1%)	72 (2%)
Other DMARD	2356 (1%)	806 (1%)	940 (1%)	796 (4%)	503 (3%)	77 (2%)
Other medical care in past year‡						
Oestrogen use among women	54 574 (27%)	19 395 (33%)	23 517 (33%)	8642 (39%)	7723 (38%)	1510 (39%)
Smoking-related illness‖	8281 (4%)	2743 (5%)	3264 (5%)	1158 (5%)	953 (5%)	197 (5%)
Hospital admission for non-cardiovascular illness	21 564 (11%)	7331 (12%)	8478 (12%)	3431 (15%)	2946 (15%)	578 (15%)
Peptic ulcer or gastrointestinal bleeding**	4261 (2%)	1180 (2%)	1408 (2%)	759 (3%)	567 (3%)	132 (3%)
Visit to emergency room because of non-cardiovascular illness	50 857 (25%)	22 062 (37%)	25 728 (37%)	7885 (35%)	7061 (35%)	1440 (37%)
Number of prescriptions, any drug (mean, SD)	49·9 (43·3)	71·8 (54·4)	70·5 (53·9)	93·2 (60·1)	91·0 (60·1)	94·2 (66·8)
Number of visits to doctor (mean, SD)	2·5 (1·6)	3·0 (1·5)	3·0 (1·5)	3·4 (1·5)	3·3 (1·5)	3·3 (1·5)

Ray WA et al. Lancet 2002, 360: 1071-1073

¿Los estudios patrocinados por la industria favorecen sus intereses?

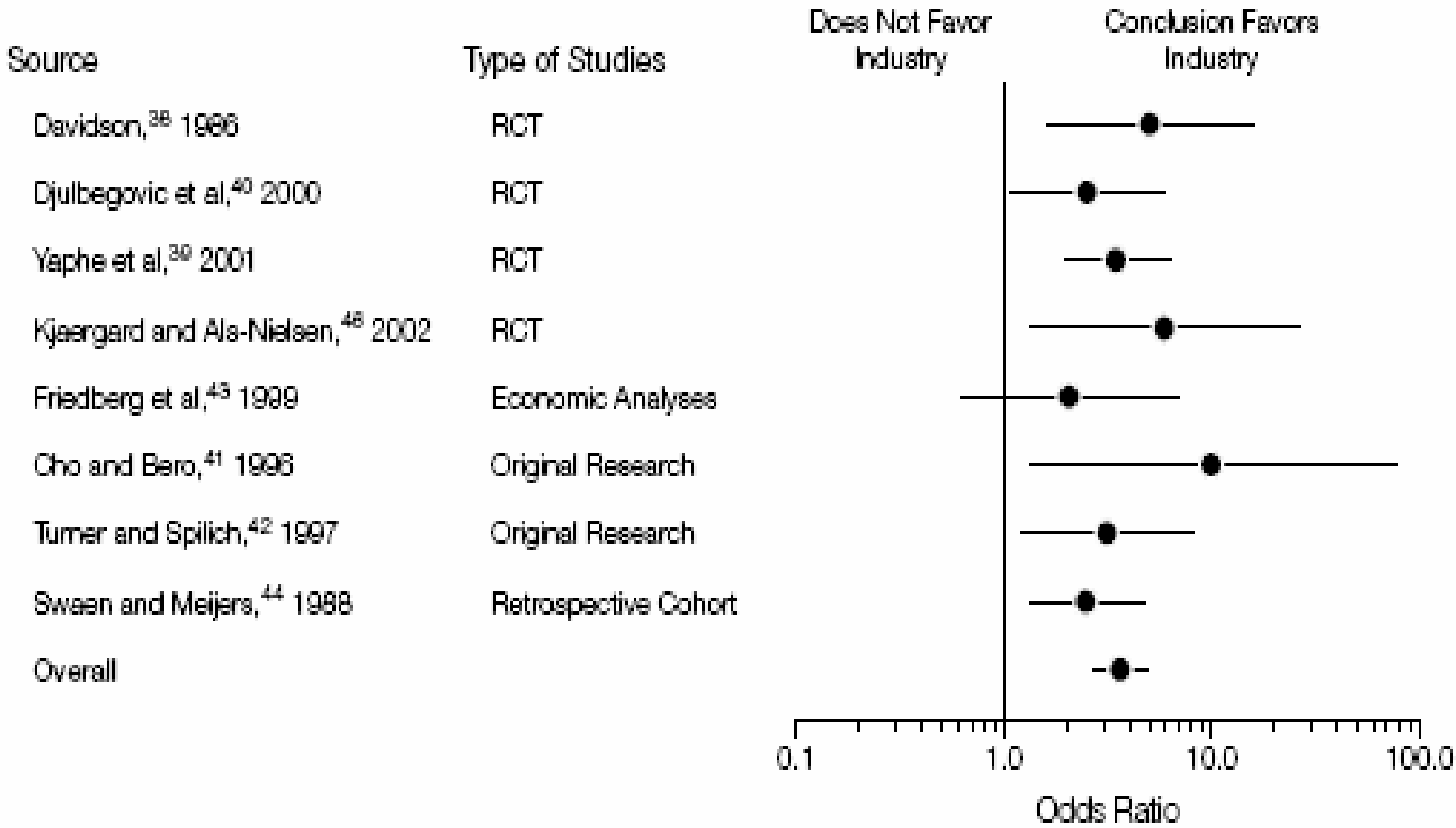
Scope and Impact of Financial Conflicts of Interest in Biomedical Research

A Systematic Review

Data Synthesis Approximately one fourth of investigators have industry affiliations, and roughly two thirds of academic institutions hold equity in start-ups that sponsor research performed at the same institutions. Eight articles, which together evaluated 1140 original studies, assessed the relation between industry sponsorship and outcome in original research. Aggregating the results of these articles showed a statistically significant association between industry sponsorship and pro-industry conclusions (pooled Mantel-Haenszel odds ratio, 3.60; 95% confidence interval, 2.63-4.91). Industry sponsorship was also associated with restrictions on publication and data sharing. The approach to managing financial conflicts varied substantially across academic institutions and peer-reviewed journals.

Bekelman JE. JAMA. 2003;289:454-465

¿Los estudios patrocinados por la industria favorecen sus intereses?



Bekelman JE. JAMA. 2003;289:454-465

¿Los estudios patrocinados por la industria favorecen sus intereses?

The NEW ENGLAND JOURNAL of MEDICINE

EARLY RELEASE

Posted February 15, 2005

ORIGINAL ARTICLE: ▶ Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention

ORIGINAL ARTICLE: ▶ Complications of the COX-2 Inhibitors Parecoxib and Valdecoxib after Cardiac Surgery

ORIGINAL ARTICLE: ▶ Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

EDITORIAL: ▶ COX-2 Inhibitors — A Lesson in Unexpected Problems

EDITORIAL: ▶ COX-2 Inhibitors — Lessons in Drug Safety

¿Los estudios patrocinados por la industria favorecen sus intereses?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 17, 2005 VOL. 352 NO. 11

Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention

Scott D. Solomon, M.D., John J.V. McMurray, M.D., Marc A. Pfeffer, M.D., Ph.D., Janet Wittes, Ph.D.,

CONCLUSIONS

Celecoxib use was associated with a dose-related increase in the composite end point of death from cardiovascular causes, myocardial infarction, stroke, or heart failure. In light of recent reports of cardiovascular harm associated with treatment with other agents in this class, these data provide further evidence that the use of COX-2 inhibitors may increase the risk of serious cardiovascular events.

Solomon SD et al. N Engl J Med 2005;352:1071-80.

¿Los estudios patrocinados por la industria favorecen sus intereses?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 17, 2005 VOL. 352 NO. 11

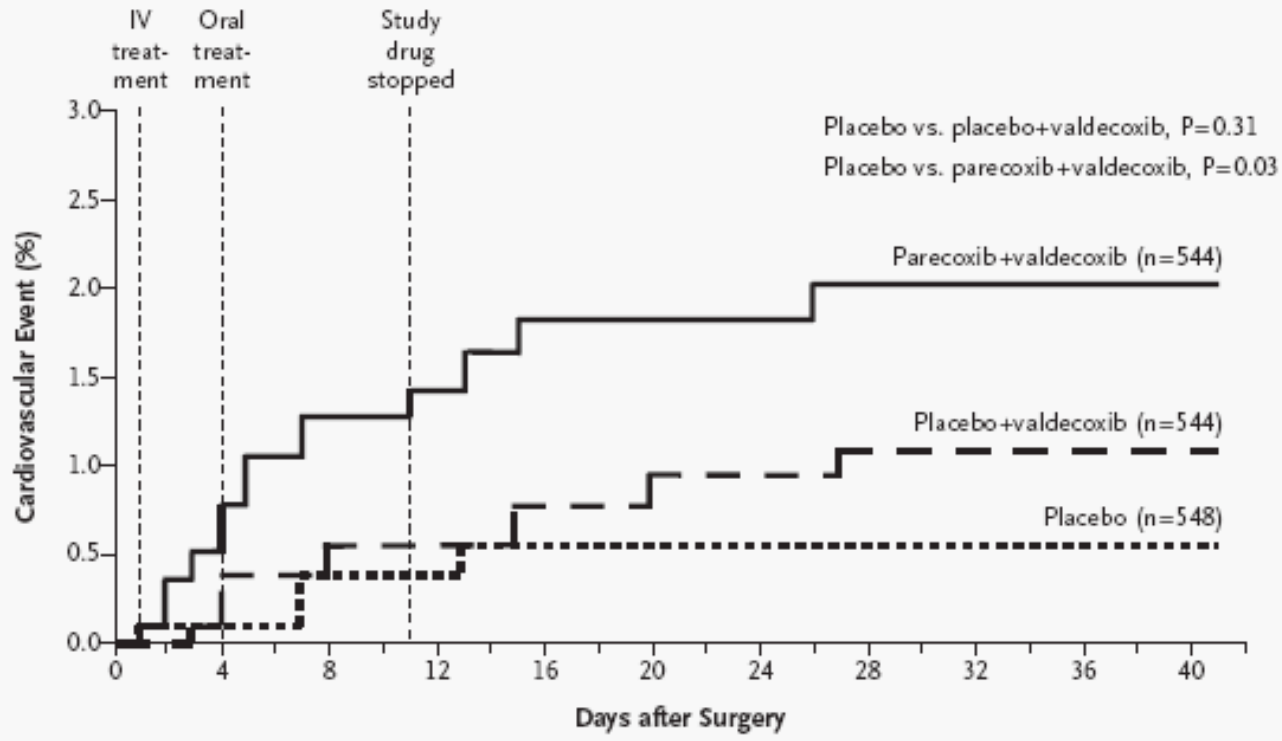
ORIGINAL ARTICLE

Complications of the COX-2 Inhibitors Parecoxib and Valdecoxib after Cardiac Surgery

Nancy A. Nussmeier, M.D., Andrew A. Whelton, M.D., Mark T. Brown, M.D., Richard M. Langford, F.R.C.A., Andreas Hoeft, M.D., Joel L. Parlow, M.D., Steven W. Boyce, M.D., and Kenneth M. Verburg, Ph.D.

Nussmeier NA et al. N Engl J Med 2005;352:1081-91.

¿Los estudios patrocinados por la industria favorecen sus intereses?



No. at Risk											
Parecoxib+valdecoxib	544	541	537	536	534	534	534	533	519	495	476
Placebo+valdecoxib	544	543	542	541	540	540	539	538	518	478	454
Placebo	548	547	546	546	545	545	545	545	525	489	475

Figure 2. Kaplan–Meier Estimates of the Time to a Cardiovascular Event.
Cardiovascular events occurred throughout and after the 10-day period of drug administration in all groups. IV denotes intravenous.

Nussmeier NA et al. N Engl J Med 2005;352:1081-91.

¿Los estudios patrocinados por la industria favorecen sus intereses?

DECLARACIÓN DE INTERESES

Supported in part by Pharmacia and Pfizer.

Dr. Nussmeier reports having served as a consultant for Pfizer and an advisory-board member for Pfizer and Novartis and having received lecture fees from Pfizer on two occasions. Dr. Whelton reports having received advisory fees from TAP Pharmaceuticals, Pfizer, GlaxoSmithKline, and Eyetech Pharmaceuticals; lecture fees from Pfizer; and consulting fees from Eyetech Pharmaceuticals. Drs. Brown and Verburg are employees of Pfizer and report owning equity and stock options in Pfizer. Dr. Langford reports having received grant support and lecture fees from Pfizer and having served on advisory boards for Pfizer and Novartis. Drs. Hoeft, Parlow, and Boyce report having received funds from Pfizer to carry out research related to this trial.

We are indebted to William K. Vaughn, Ph.D., for providing statistical support and to Stephen N. Palmer, Ph.D., E.L.S., for editorial assistance.

Nussmeier NA et al. N Engl J Med 2005;352:1081-91.

¿Los estudios patrocinados por la industria favorecen sus intereses?

European Medicines Agency

For the other COX-2 inhibitors (celecoxib, etoricoxib, lumiracoxib and parecoxib), the Committee agreed that the available data show an increased risk of thrombotic adverse cardiovascular reactions, such as heart attacks and strokes. The CHMP confirmed its February 2005 finding of an association between duration and dose of intake and the probability of suffering such cardiovascular reactions. The Committee also confirmed that serious skin reactions occur with other COX-2 inhibitors, but have been reported at lower rates than with Bextra. In concluding its review, the CHMP recommended the following contraindications and precautions for these products:

- Contraindications stating that COX-2 inhibitors must not be used in patients with established ischaemic heart disease and/or cerebrovascular disease (stroke), and also in patients with peripheral arterial disease
- Reinforced warnings to healthcare professionals to exercise caution when prescribing COX-2 inhibitors to patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking
- Given the association between cardiovascular risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment
- Additional or strengthened warnings to healthcare professionals and patients that hypersensitivity reactions and rare, but serious and sometimes fatal, skin reactions can occur with all COX-2 inhibitors. In the majority of cases these occur in the first month of use, and prescribers are warned that patients with a history of drug allergies may be at greater risk.

¿Los estudios patrocinados por la industria favorecen sus intereses?

BMJ

US heart group says COX 2 inhibitors should be last choice for pain relief in patients at risk

Susan Mayor

BMJ 2007:334:441-

CURRENT OPINION

Drug Safety 2005; 28 (3): 183-189
0114-5916/05/0003-0183/$34.95/0

Do Selective Cyclo-Oxygenase-2 Inhibitors Have a Future?

Bernard Bannwarth

Department of Rheumatology, Pellegrin Hospital and Division of Therapeutics, Victor Segalen University, Bordeaux, France

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.
Learn and Live.

Use of First- and Second-Generation Cyclooxygenase-2–Selective Nonsteroidal Antiinflammatory Drugs and Risk of Acute Myocardial Infarction

Frank Andersohn, Samy Suissa and Edeltraut Garbe

Circulation 2006;113;1950-1957; originally published online Apr 17, 2006;

Mayor S. BMJ 2007. Andersohn F. Circulation 2006. Bannwarth B. Drug Safety 2006

¿Los estudios patrocinados por la industria favorecen sus intereses?

DECLARACIÓN DE INTERESES

El Dr. Reuben se inventó datos de ensayos clínicos sobre dolor postoperatorio y tenía publicaciones en Anesthesia & Analgesia y en Anesthesiology. Ambas revistas borraron sus publicaciones.

◆ EDITORIAL VIEWS **By James C Eisenach, MD, Editor-in-Chief, ANESTHESIOLOGY**

Anesthesiology 2009; 110:955–6

Data Fabrication and Article Retraction

How Not to Get Lost in the Woods

further research needed to prove or refute published information obtained from likely fictitious data (NSAIDs, celecoxib, rofecoxib, venlafaxine, i.v. blocks, combinations, etc)

Eisenach JC. Anesthesiology 2009;110:955-6.

¿Son de mala calidad los estudios patrocinados por la industria?

Pharmaceutical industry sponsorship and research outcome and quality: systematic review

Joel Lexchin, Lisa A Bero, Benjamin Djulbegovic, Otavio Clark

What is already known on this topic

When a pharmaceutical company funds research into drugs, studies are likely to produce results favourable to the sponsoring company's product

What this study adds

Research funded by drug companies was more likely to have outcomes that favour the sponsor's product than research funded by other sources

This cannot be explained by the reported quality of the methods in research sponsored by industry

The result may be due to inappropriate comparators or to publication bias

Lexchin J. BMJ 2003;326:1167–70

¿La industria investiga en enfermedades que se inventa?

Selling sickness: the pharmaceutical industry and disease mongering

Ray Moynihan, Iona Heath, David Henry

A lot of money can be made from healthy people who believe they are sick. Pharmaceutical companies sponsor diseases and promote them to prescribers and consumers. Ray Moynihan, Iona Heath, and David Henry give examples of "disease mongering" and suggest how to prevent the growth of this practice

- **Convertir situaciones cotidianas en enfermedades: Calvicie.**
- **Vender somatizaciones como enfermedades: Fibromialgia.**
- **Pasar problemas personales a enfermedad: Depresión o tristeza.**
- **Conceptualizar riesgos como enfermedades: Osteoporosis.**
- **Maximizar la prevalencia de la enfermedad: Disfunción erectil.**

Moynihan R. BMJ 2002;324:886–91

¿La industria investiga en enfermedades que se inventa?

Moynihan R. BMJ 2002;324:886–91

Conclusiones ¿Hay luz al final del tunel?

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

COX-2 Inhibitors — A Lesson in Unexpected Problems

Jeffrey M. Drazen, M.D.

COX-2 Inhibitors — Lessons in Drug Safety

Bruce M. Psaty, M.D., Ph.D., and Curt D. Furberg, M.D., Ph.D.

Drazen JM, Pasaty BM. N Engl J Med 2005;352:1133-35

¿Hay luz al final del tunel?

- Los médicos se sienten “engañados”.
- Las compañías farmacéuticas están avergonzadas y tienen riesgos financieros.
- Los pacientes han sido maltratados.
- Las agencias reguladoras están cuestionadas.
- ¿Se pueden prevenir estos problemas en el futuro?

Patients and the public deserve big changes in evaluation of drugs

Garattini S. BMJ 2009;338:804–806

¿Cuál es el marco legal en I+D que regula esta relación?

LEY 29/2006, DE 26 DE JULIO, DE GARANTÍAS Y USO RACIONAL DE LOS MEDICAMENTOS Y PRODUCTOS SANITARIOS
(BOE núm. 178, de 27 julio [RCL 2006, 1483])

REAL DECRETO 2000/1995, DE7 DE DICIEMBRE, POR EL QUE SE MODIFICA EL REAL DECRETO 767/1993, DE 21 DE MAYO, QUE REGULA LA EVALUACIÓN, AUTORIZACIÓN, REGISTRO Y CONDICIONES DE DISPENSACION DE ESPECIALIDADES FARMACEUTICAS Y OTROS MEDICAMENTOS DE USO HUMANO FABRICADOS INDUSTRIALMENTE
(BOE núm. 11, de 12 enero [RCL 1996, 105])

REAL DECRETO 223/2004, DE 6 DE FEBRERO, POR EL QUE SE REGULAN LOS ENSAYOS CLÍNICOS CON MEDICAMENTOS
(BOE núm. 33, de 7 febrero [RCL 2004, 325])

REAL DECRETO 1338/2006, DE 21 DE NOVIEMBRE, POR EL QUE SE DESARROLLAN DETERMINADOS ASPECTOS DEL ARTÍCULO 93 DE LA LEY 29/2006, DE 26 DE JULIO, DE GARANTÍAS Y USO RACIONAL DE LOS MEDICAMENTOS Y PRODUCTOS SANITARIOS EN EL MARCO DEL SISTEMA DE PRECIOS DE REFERENCIA
(BOE núm. 279, de 22 noviembre [RCL 2006, 2092])

Conclusiones: Colaboración necesaria pero con cambios

Patients and the public deserve big changes in evaluation of drugs

- La evaluación de fármacos ha de ser más transparente.
  - Pacto con las agencias del plan de investigación.
  - Revisión previa de los protocolos y contrato por los CEIC.
  - Declaración de intereses.
  - Libre acceso a todos los datos de los ensayos clínicos.
  - Publicación de todos los datos de los ensayos clínicos.
- Evaluación fármacos realizada por expertos independientes.

Garattini S. BMJ 2009;338:804–806

Conclusiones: Colaboración necesaria pero con cambios

Patients and the public deserve big changes in evaluation of drugs

- Fomentar los estudios de farmacovigilancia y observacionales.
- Necesidad de demostrar el valor añadido de las NEQ o NEB.
- Comentar los casos de conflicto de intereses abiertamente.
- Fomentar los cambios con un incremento de duración patente.

Garattini S. BMJ 2009;338:804–806