

Morgan Lewis

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Regulatory Trends Affecting Product Approvals and Reimbursement of Drugs and Biologics



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I. Changing Scope of U.S. Regulatory Trends

- Enhanced focus by FDA on drug safety issues
- New focus by Centers for Medicare and Medicaid Services (CMS) on safety and comparative effectiveness for coverage/reimbursement
- Pending new legislation affecting drug safety
- Consequent significant effects on drug development and reimbursement, and on market valuation of products and companies

Of 100 drugs

for which investigational new applications
are submitted to the Food and Drug
Administration . . .

70*

will successfully complete Phase 1 human
trials — which last several months and
mainly test safety — and go on to Phase 2.

will complete Phase 2 —
which can last up to
two years and mainly
tests effectiveness —
and go to Phase 3.

will clear Phase
3, which can last
up to four years
and tests safety,
dosage and
effectiveness.

33*

25 to 30*

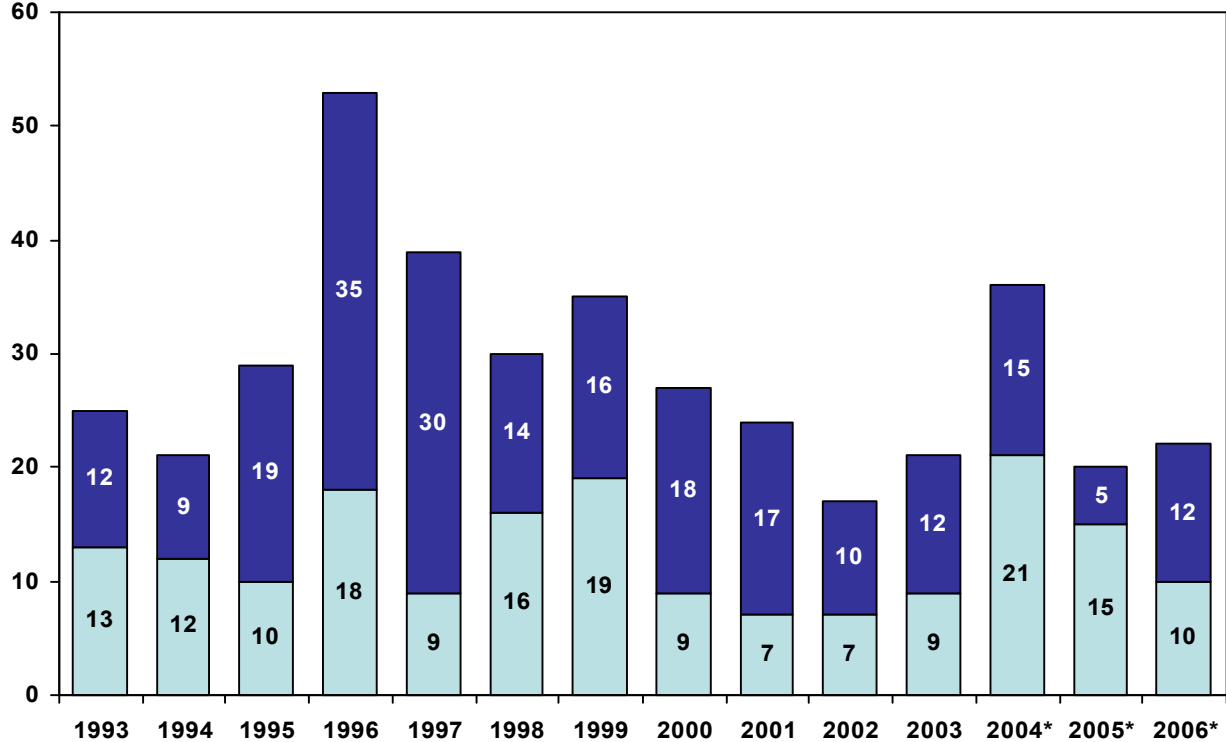
20*

will ultimately
be approved
for sale.

* On average

Source: FDA

CDER New Molecular Entity and New Biologic Approvals by Calendar Year*



Priority NME Approvals

Standard NME Approvals

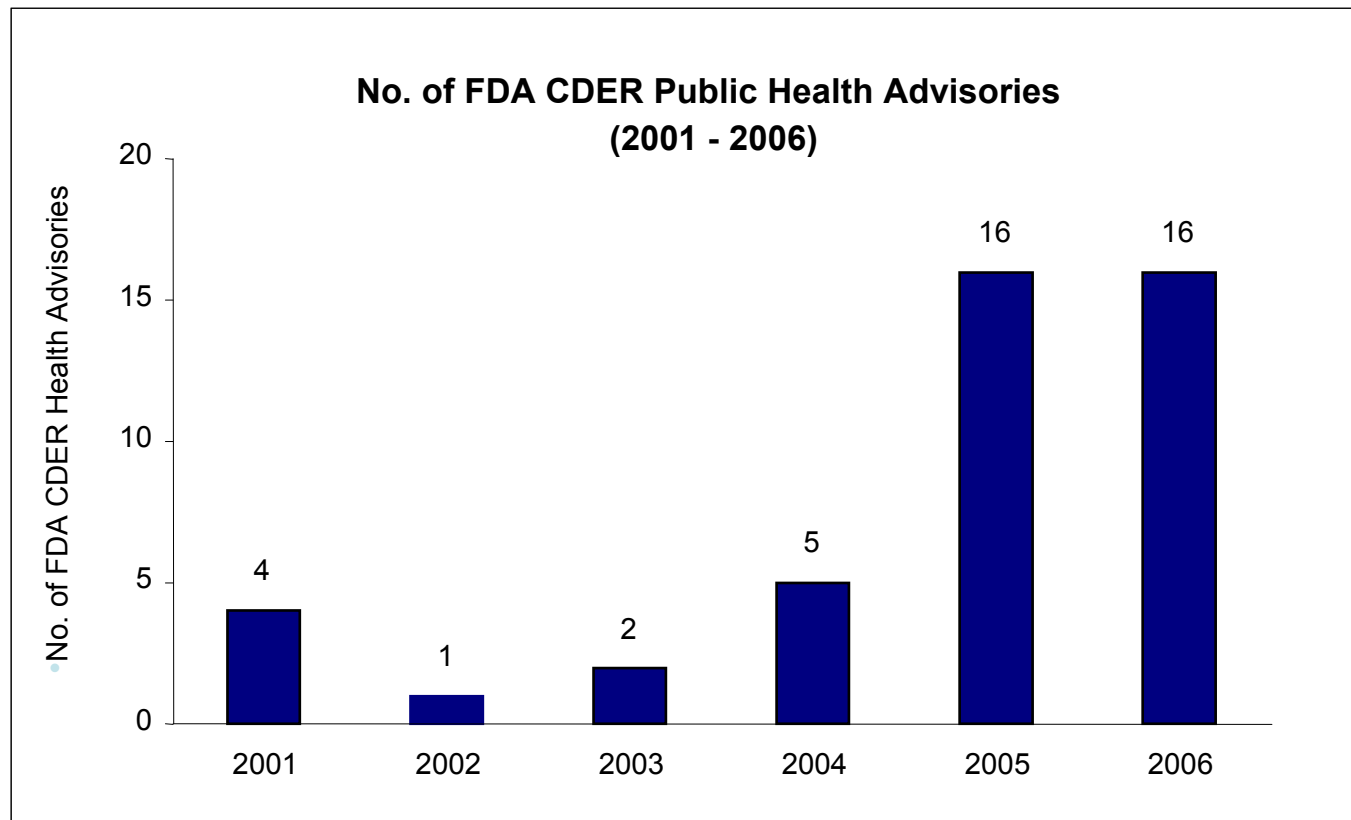
Number of NMEs Filed

Source: FDA (*Beginning in 2004 these figures include new BLAs for therapeutic biologic products transferred from CBER to CDER)

II.(A) Enhanced Focus by FDA on Drug Safety

- Rejection or delay of new drug application (NDA) approvals relating to safety concerns
 - Merck/Arcoxia; Sanofi-Aventis/Acomplia; Wyeth/Pristiq; GlaxoSmithKline & Pozen/Trexina
- Conditioning NDA approvals on post-market trials (Phase IV studies)
- Issuance of safety alerts
 - GlaxoSmithKline/Avandia; Takeda/Actos; Cephalon/Fentora; AstraZeneca/Prilosec & Nexium

Enhanced Focus by FDA on Drug Safety (cont'd)



Enhanced Focus by FDA on Drug Safety (cont'd)

- Requiring label revisions
 - Erythropoiesis-stimulating agents (ESAs)
 - Amgen/Aranesp & Epogen; Johnson & Johnson/Procrit
 - Updated warnings, new boxed warning and dosing instructions
- Suggesting additional clinical trials
 - FDA Oncologic Drugs Advisory Committee (May 2007) unanimously recommended additional safety studies for ESAs to support continued oncologic marketing
 - FDA Cardiovascular and Renal Drugs Advisory Committee (Sept. 2007) recommendation for post-marketing safety studies of Bayer's Trasyolol

Enhanced focus by FDA on Drug Safety (cont'd)

- Imposition of restricted distribution programs
 - Biogen Idec & Elan/Tysabri (June 2006)
 - FDA guidance documents on risk minimization action programs (RiskMAPs) (March 2005)
- Removal of previously-approved indications
 - Sanofi-Aventis/Ketek
- Market Withdrawals
 - Merck/Vioxx; Novartis/Zelnorm
 - Zelnorm requested by FDA to be withdrawn notwithstanding that only 0.1% (13) of patients had serious events out of 11,614 treated

II.(B) Recent FDA Actions Regarding Drug Safety

- Establishing new Drug Safety Board (March 2007), to provide independent oversight and advice to FDA on drug safety issues and disseminating safety information.
- Establishing new associate directors for safety in all 17 FDA drug review divisions
- Initiating a new pilot program to prepare safety profiles for several approved new molecular entities
- Establishing a new Risk Communication Advisory Committee to assist the Agency in communicating risks and benefits to the public
- Initiating planning to integrate genomic information into drug prescribing
- New FDA *Drug Safety Newsletter* (Sept. 2007), to report early safety findings

II.(C) Industry Response Regarding Drug Safety

- Announcement (Sept. 27, 2007) by seven pharma companies of a new alliance, the International Serious Adverse Events Consortium, to sponsor research on genetic markers to predict which people are at risk for serious drug-related adverse events
 - FDA will work with the consortium

III. CMS Activities Regarding Drug Safety and Reimbursement

- New focus by CMS on relation of drug safety and effectiveness to coverage and reimbursement
 - Impetus from desire to develop cost-containment mechanisms following substantial increase in government reimbursement costs for the new Medicare prescription drug benefit (Jan. 2006)
- Potential for restriction of coverage and reimbursement
 - Restrictions on coverage of ESAs for certain cancer patients, in view of FDA's imposition of a new black box label warning for this therapeutic class (July 2007)

CMS Activities Regarding Drug Safety and Reimbursement (cont'd)

- cost of these drugs to Medicare was \$2 billion in 2006, its largest single therapeutic expenditure
- Clinical Trial design
 - Consideration of limiting reimbursement for ESAs only to patients enrolled in appropriately designed clinical research studies
 - Makes CMS another regulatory agency to be considered in developing clinical trials
- Comparative effectiveness studies
 - Impending report by Congressional Budget Office on potential for comparative effectiveness research to reduce costs and improve treatment

CMS Activities Regarding Drug Safety and Reimbursement (cont'd)

- Proposals to establish a new, quasi-governmental agency to oversee comparative research, possibly linked to the Agency for Healthcare Research and Quality (AHRQ)
 - Similar focus to U.K.'s National Institute for Health and Clinical Excellence
- First comparative effectiveness trial of two pioneer drugs, by National Institutes of Health (announced Feb. 2007)
 - Comparative trial of two Genentech drugs (Lucentis - \$2,000/dose and Avastin - \$40/dose)
 - Both are variations of an ocular vascular endothelial growth factor inhibitor, but approved for different indications
 - Potential Medicare savings in the event that the less expensive drug could be used for both indications estimated by CMS at \$1 billion/year

IV. New Drug Safety Legislation

- Food and Drug Administration Amendments Act of 2007 (H.R.3580) – signed by the President (Sept. 27, 2007)
 - Provides FDA with authority to require a drug or biologic to have a Risk Evaluation and Mitigation Strategy (REMS) if serious risks are found
 - Provides FDA with the power to require labeling changes
 - Requires manufacturers to post certain information on a public clinical trials registry data book
 - Requires that FDA create a post-market surveillance system
 - Provides for civil penalties of up to \$10 million for certain violations
- The new legislation is expected to create new interactions among FDA, CMS, and private payers regarding drug utilization

V. Effects of FDA and CMS Regulatory Trends

- Effects on product selection and development
 - “Me-too” NDAs may be held to a high FDA approval standard
 - FDA Arthritis Drugs Advisory Committee for Arcoxia concluded “approval of an additional NSAID is only warranted if a compound can demonstrate a unique therapeutic value.”
 - Replacement of an existing drug with a new drug with a better safety profile
 - FDA request to cease marketing Pfizer’s Rezulin for new, assertedly safer alternatives, Avandia and Actos

Effects of FDA and CMS Regulatory Trends (cont'd)

- Focus by FDA on continuous assessment of risk/benefit profiles of marketed drugs
- Drug developers will have to evaluate whether to enroll more patients in clinical trials to address potential safety issues
- Potential for more restricted distribution, and consequently, sales
- Effects on product and company valuation
 - FDA actions based on safety concerns could have a significant impact on the market valuation of the affected products and companies

Effects of FDA and CMS Regulatory Trends (cont'd)

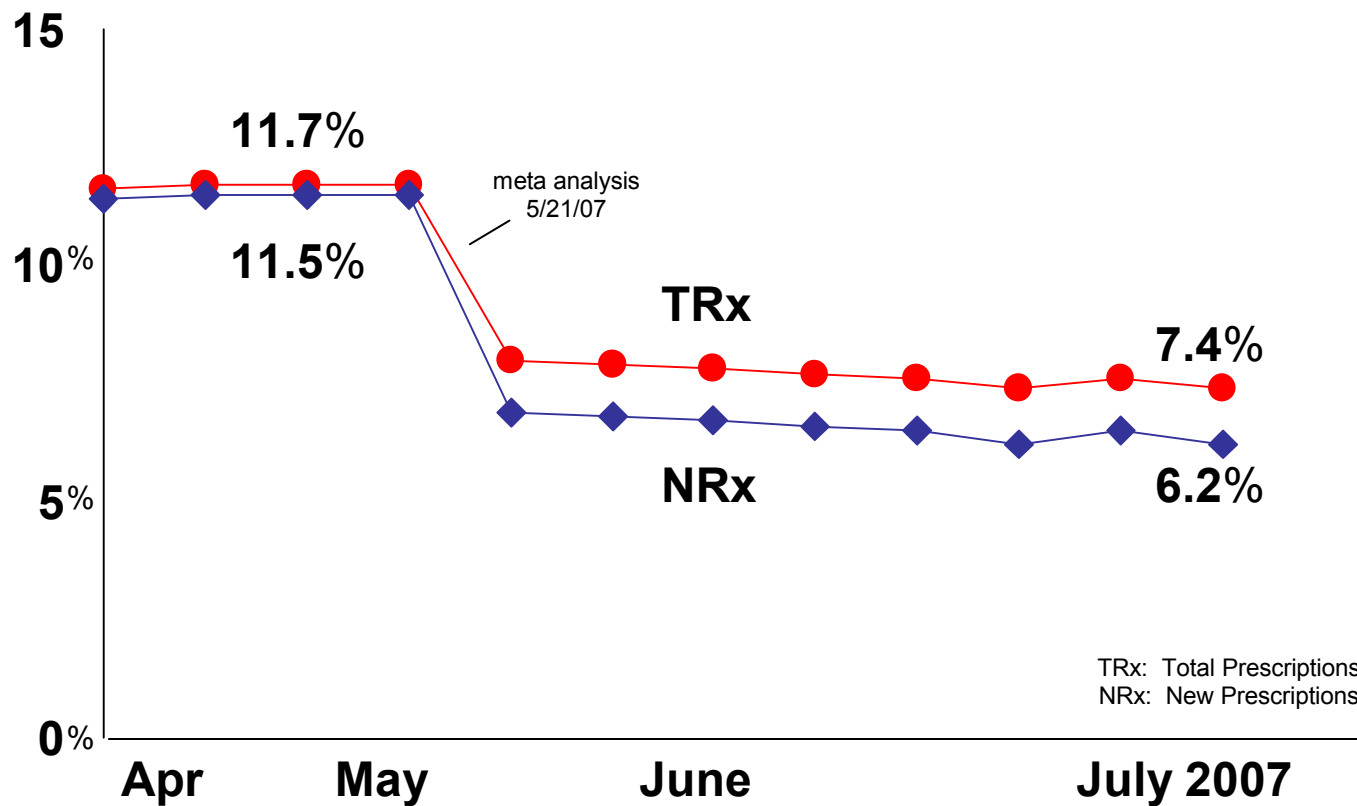
Effect of FDA safety actions on market valuations of selected drug products and companies

Product	Company	Product Sales and Effect of FDA Safety Actions
Zelnorm	Novartis	<ul style="list-style-type: none"> •U.S. Zelnorm sales were \$488 million in 2006. •Due to the suspension, the loss in sales on budgeted 2007 basis is estimated to be more than \$600 million.
Aranesp and Epogen	Amgen	<ul style="list-style-type: none"> • Aranesp sales were \$654 million, Epogen \$625 million, for first quarter of 2007 in U.S. • Amgen has begun taking actions to reduce operating expense growth in order to offset any decline in revenues, and may defer or possibly cancel previously planned clinical trials in order to adjust its R&D investment plans.
Procrit	Johnson & Johnson	<ul style="list-style-type: none"> • Sales for the third quarter of 2007 are expected to decrease 8% to \$482 million.
Avandia	GlaxoSmithKline	<ul style="list-style-type: none"> • A lawsuit was filed in June 2007 claiming Glaxo failed to warn of the drug's heart risks. • Market share reductions.

The Avandia Damage

GSK's data on script trends for its blockbuster antidiabetic brand in the weeks following a drug safety scare.

US retail oral anti-diabetic volume – market share



Source: RPM Report (Sept. 2007)

Effects of FDA and CMS Regulatory Trends (cont'd)

- Increasing importance of discussions with CMS at the clinical trial stage on reimbursement categorization of a product's intended indications
- Potential adverse effects on negotiations and decisions on collaboration agreements and M&A from these regulatory trends
 - Termination by Pfizer of co-development agreement with Organon for asenopine (Dec. 1006)
 - Pfizer assertion of comparative effectiveness information as the most important factor in deciding whether to continue a compound's development
- Increasing interest in development of comparative effectiveness studies, which may lead to reductions in coverage and reimbursement levels

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