

How Are New Safety Concerns Affecting FDA Approvals and CMS Reimbursement of Bio/Pharma Products



Stephen Paul Mahinka
smahinka@morganlewis.com

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
- 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*

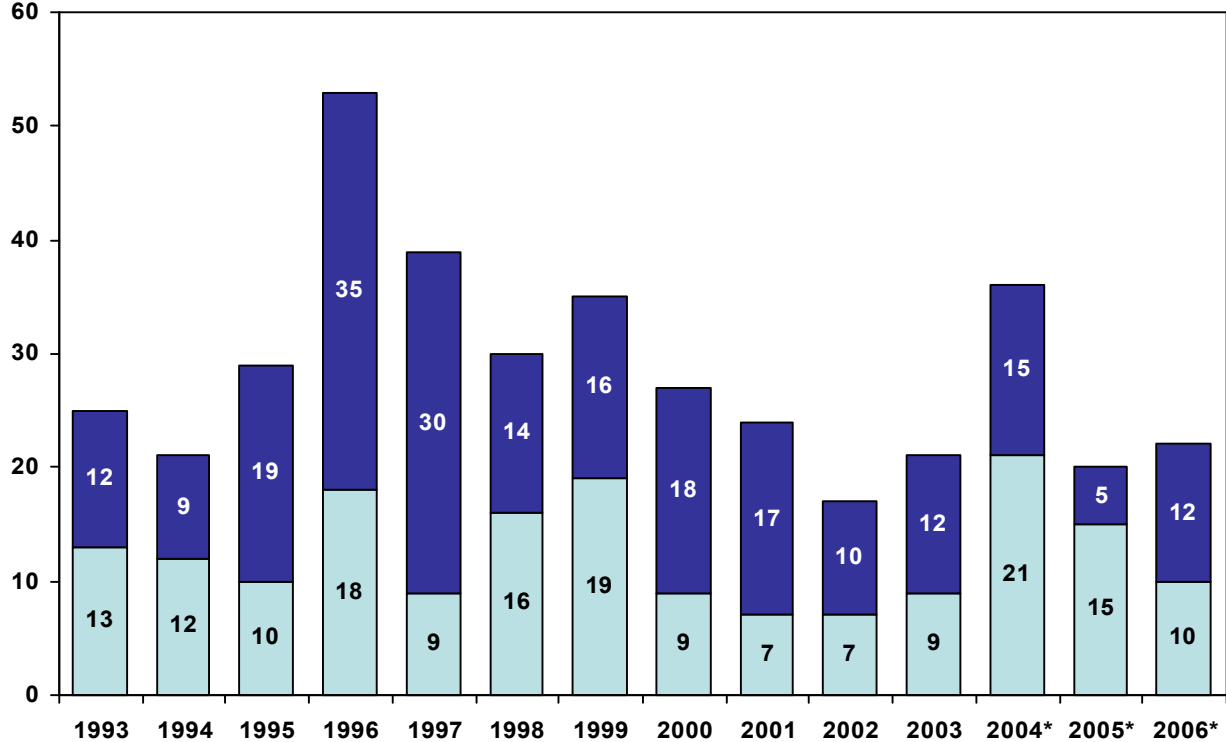
20*

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

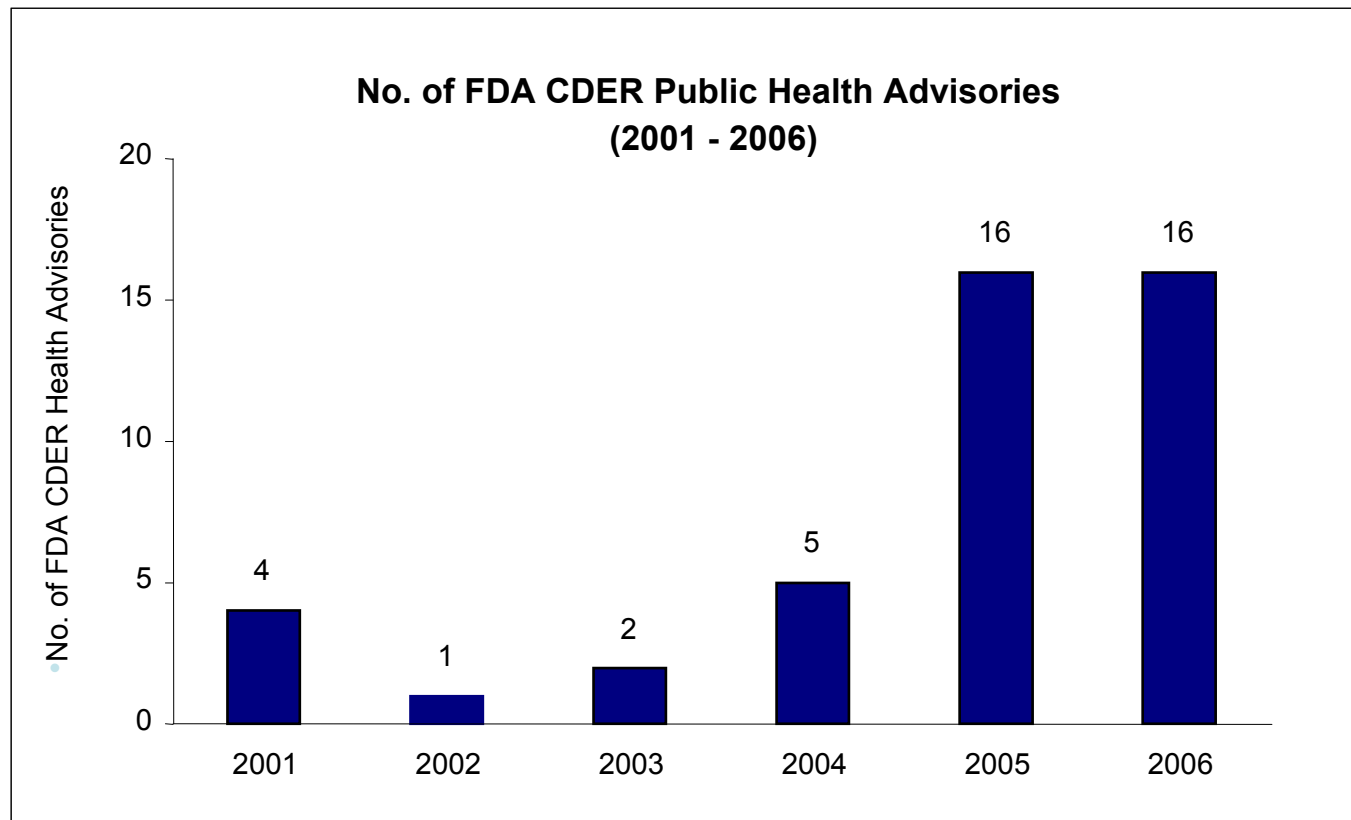
Number of NMEs Filed

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 recently of new drug application (NDA) approvals relating to safety concerns
 - Merck/Arcoxia; Sanofi-Aventis/Acomplia; Wyeth/Pristiq & Viviant & bifeprunox; GlaxoSmithKline & Pozen/Trexina; GlaxoSmithKline/Gepirone ER; Novartis/Prexige & Galvus
- Conditioning NDA approvals on post-market trials (Phase IV studies)
- Issuance of safety alerts
 - GlaxoSmithKline/Avandia; Takeda/Actos; Cephalon/Fentora & Provigil; AstraZeneca/Prilosec & Nexium

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



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

- Requiring label revisions/warnings
 - Erythropoiesis-stimulating agents (ESAs)
 - Amgen/Aranesp & Epogen; Johnson & Johnson/Procrit
 - Updated warnings, new boxed warning and dosing instructions
 - Eli Lilly/Zyprexa & Symbyax
 - Bristol-Myers Squibb/Definity & GE Healthcare/Optison (ultrasound contrast drugs)

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

- 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; Novartis & Genentech/Xolair
 - FDA guidance documents on risk minimization action programs (RiskMAPs) (March 2005)
- Removal of previously-approved indications
 - Sanofi-Aventis/Ketek
- Market Withdrawals
 - Merck/Vioxx; Bayer/Trasylol; 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 Responses 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
- Criticisms of FDA's enhanced focus on drug safety as unduly delaying product approvals by CEOs of Novartis & Wyeth
 - Dr. Kenneth Kaitin, Director of the Tufts University Center for the Study of Drug Development: "It's harder and harder to bring a new product to the market. [In addition to the decrease in the industry's R&D productivity, FDA] has adopted a more risk averse, cautious approach to drug approvals." (Nov. 7, 2007).

III. 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 data registry
 - 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
 - Dr. Mark S. McClellan, former head of both FDA and CMS: the new legislation “is going to be the biggest set of changes in post-market drug regulation since at least 1962.”

IV. 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 and reimbursement 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)
 - First time CMS has restricted coverage based on FDA safety concerns

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
- Challenges by medical societies and patient advocacy groups, and introduction of legislation, in opposition to CMS' restrictions
- FDA letter to Congress supporting CMS' action as "generally consistent" with available scientific data (Oct. 12, 2007)
- At least one large private insurer, Aetna, has altered its coverage to mirror the restrictions imposed by CMS

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

- Comparative effectiveness studies
 - Report by Congressional Research Service on potential for comparative effectiveness research to reduce costs and improve treatment (Oct. 15, 2007)
 - Notes that Congress could improve efficiency and coordination of comparative effectiveness studies by designating one entity to oversee the research
- Proposals to establish a new, quasi-governmental agency to oversee comparative research, possibly linked to the Agency for Healthcare Research and Quality (AHRQ)
 - Supported by various entities, including Medicare Payment Advisory Commissions (MedPAC) in its June 2007 report, the trade group America's Health Insurance Plans, and the Director of the Congressional Budget Office
 - Similar focus suggested as that of the U.K.'s National Institute for Health and Clinical Excellence

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

- 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; Avastin prescribed off-label for eye disease uses
 - Potential Medicare savings in the event that the less expensive drug could be used for both indications estimated by CMS at \$1 billion/year
 - Genentech's proposal (Oct. 2007) to limit the availability of Avastin to pharmacy compounders for off-label eye disease uses has been delayed following opposition by the American Academy of Ophthalmology and the American Society of Retinal Specialists

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 longer clinical trials to address potential safety issues
- More and earlier information availability on clinical trials, resulting in earlier, and perhaps premature, risk-benefit assessments
- Increasing importance of discussions with CMS at the clinical trial stage on reimbursement categorization of a product's intended indications

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

- Effects on other payors of FDA safety concerns
 - Adoption of mirror restrictions on coverage and reimbursement by private insurers
 - Potential for restrictions by other government purchasers
 - Decision by Department of Veterans Affairs on October 5, 2007 to severely limit the use of Avandia by removing it from its formulary, because of safety concerns
- Effects on product and company valuation
 - Potential for more restricted distribution, and consequently, sales
 - 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)

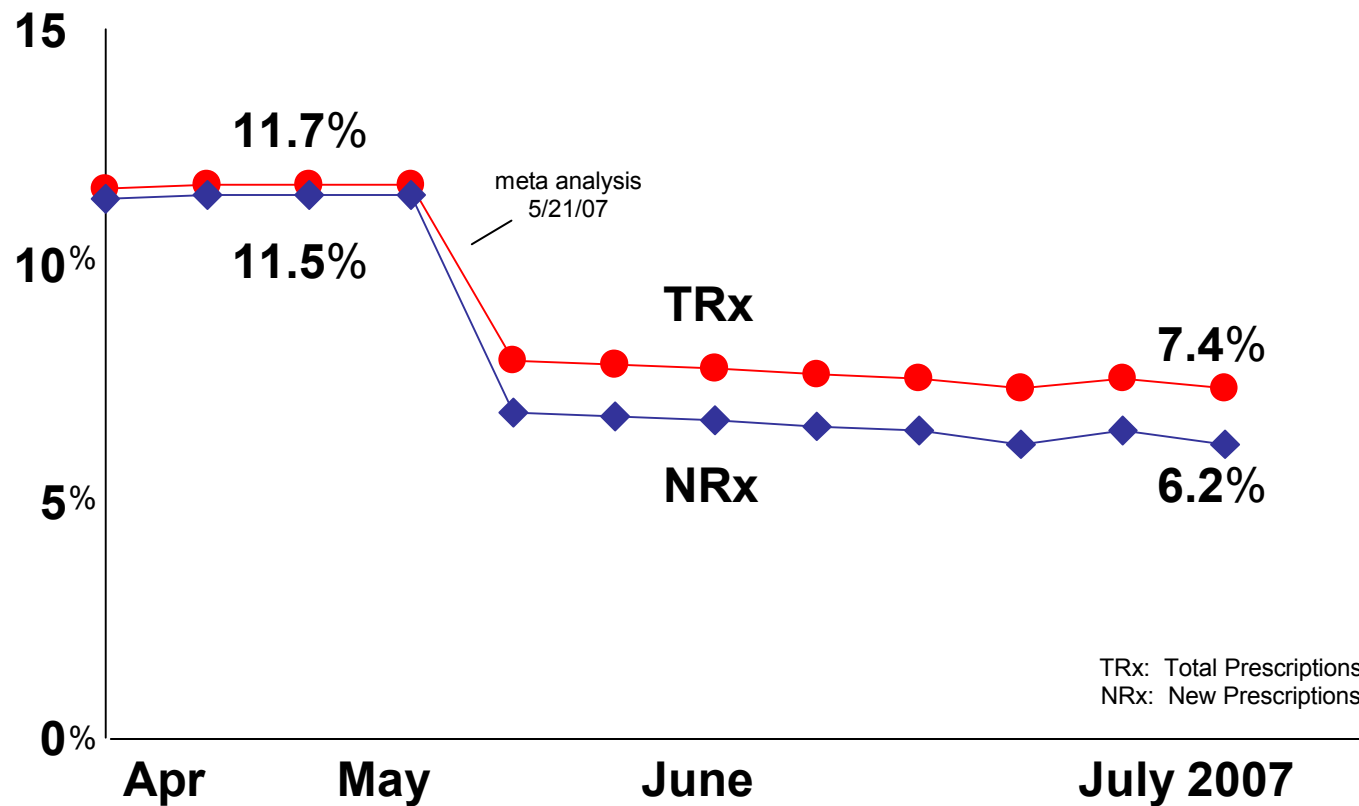
Effect of FDA safety actions on market valuations of selected drug products and companies

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 decreased 23% and sales of Epogen decreased 5% for the third quarter of 2007 in U.S.; third quarter profit fell 82%. • Amgen has begun taking actions to reduce operating expense growth in order to offset any decline in revenues, including layoffs, 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%.
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. Third quarter U.S. sales fell 48%.

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)

- Need to develop a risk management strategy which incorporates, during the clinical trial phases, tests designed to establish comparative safety and effectiveness, and cost effectiveness
- Need to develop clinical testing and communications strategies and respond to the results of institutional comparative or other studies, and to consider the implications of making supporting data more publicly available at an earlier stage in the product's lifecycle
- Need to prepare action plans to address questionably-supported calls for market restrictions or imposition of REMS, or non-approval or market withdrawal, of products, and the potential for resulting class action litigation challenges

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

- 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. 2006)
 - Pfizer assertion of comparative effectiveness information as the most important factor in deciding whether to continue a compound's development
- Development of institutional entities to produce comparative effectiveness studies, which can be expected to lead to reductions in coverage and reimbursement levels by the government and private payors

Regulatory Trends Affecting Product Approvals and Reimbursement of Drugs and Biologics



Stephen Paul Mahinka
smahinka@morganlewis.com