

Critical Regulatory Concerns That MUST Be Addressed in a Life Sciences M&A



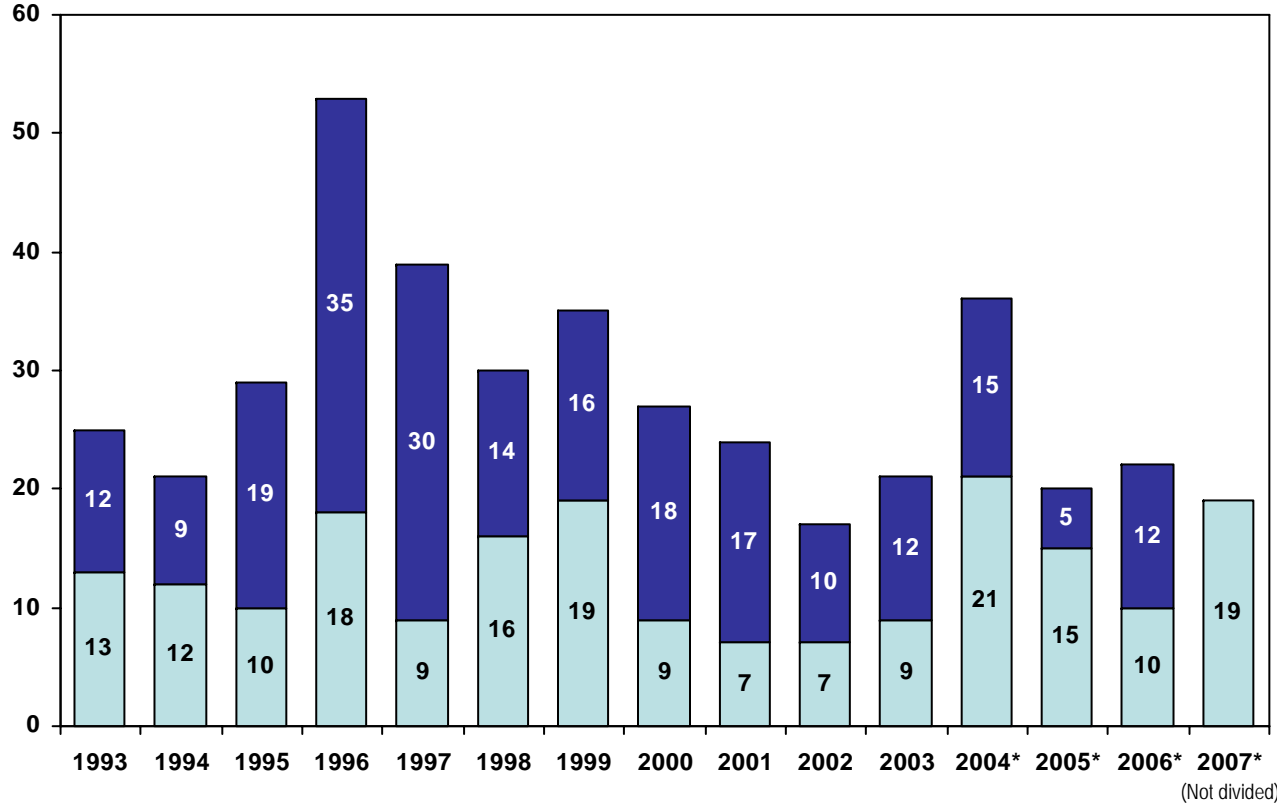
Stephen Paul Mahinka
smahinka@morganlewis.com

American Conference Institute
New York, NY

Changing Focus and Impact of Regulatory Issues in Life Sciences M&A

- Enhanced focus of FDA on safety concerns
- New significance of CMS pricing/reimbursement issues
- Resulting effects of new regulatory focus and concerns on company/product valuation

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

1. *Assessing the Target's FDA Regulatory Status*

- Products
 - Investigational
 - Marketed
- Operations
 - Manufacturing
 - Marketing/Promotion
 - Distribution

Assessing the Target's FDA Regulatory Status – Investigational Products

- Review status – preclinical studies, phase I, II or III studies, and pending marketing applications
 - Review recent public statements by the target
 - Review IND documents and/or pending marketing applications (NDA/BLA)
 - IRB approval requirements
 - IND reporting obligations
 - Informed consents
 - Protocol amendments/Special Protocol Assessments
 - FDA correspondence/meeting minutes

Assessing the Target's FDA Regulatory Status – Investigational Products

- Compliance
 - Care and Use of Laboratory Animals regulations
 - Good Laboratory Practices (GLPs) regulations
 - Good Clinical Practices (GCPs) regulations
 - Clinical holds/studies halted voluntarily/recalls
 - Auditing of records by FDA
 - Foreign trials
 - Clinical Monitoring
 - Posting of results on clinicaltrials.gov
 - Inspections of CRO or clinical site/investigator
 - Financial disclosure
 - No debarred individuals/entities
 - Pre-approval promotion

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

Assessing Target's FDA Regulatory Status – Marketing Applications

- Status of all pending and approved U.S. and foreign marketing applications (NDAs/BLAs/505(b)(2))
- Review Establishment Registration and Drug Listing status
- Prescription Drug User Fee Act payments
- Annual Reports

Assessing the Target's FDA Regulatory Status - Marketed Products

- Review of scope of approval or other regulatory basis for marketing
 - Determine basis of marketing (NDA, BLA, OTC monograph, grandfather status)
 - Review any Drug Master Files (DMFs)
- Scope of indications
 - Contraindications; limited patient population; other express limitations
- Review any RiskMAP / REMS imposed
 - FDA guidance on risk management programs (March 2005)
 - e.g., Biogen Idec/Elan – Tysabri; Novartis/Genentech - Xolair

Assessing the Target's FDA Regulatory Status - Manufacturing Compliance

- Compliance with Good Manufacturing Practice (GMP) regulations
 - Review audits, inspection history (FD 483s), GMP manual, state licensure
- If contract manufacturing
 - Review contract, complaints, audits, master files, FDA inspections history
- Review compliance for both finished pharmaceuticals and active pharmaceutical ingredients (APIs)
- Review manufacturing costs/API availability
- Review adverse experience reports (AERs), pharmacovigilance data, complaints

Assessing the Target's FDA Regulatory Status - Marketing/Promotion Compliance

- Compliance with FDA marketing requirements
 - Promotion consistent with indications
 - Review of sales/marketing materials
 - Review detail force/MSLs training materials
- Review FDA Warning Letters/untitled letters, other compliance actions
- Review direct-to-consumer (DTC) promotion
- Review off-label information dissemination

Assessing the Target's FDA Regulatory Status - Distribution Compliance

- Compliance with Prescription Drug Marketing Act (PDMA)
- Review FDA inspection/compliance history
- Review compliance with state licensure requirements for distribution facilities
- Controlled substances
 - Review Drug Enforcement Administration (DEA) compliance

2. Evaluating the Target's Lifecycle Management

- Review patent status
- Review patent term extension status (potential up to 5 years)
- Review any 5-year market exclusivity for new chemical entities (NCEs) under Hatch-Waxman Amendments
- Review any 3-year market exclusivity for new indications/applications under Hatch-Waxman Amendments (e.g., Rx-to-OTC use)

Evaluating the Target's Lifecycle Management

- Review Orphan Drug exclusivity (7 years)
- Review pediatric exclusivity (6 months)
- Review generic drug 180-day exclusivity
- Review authorized generics
- Review product extension filings (new dosages/indications/routes of administration)
- Review follow-on products (e.g., Clarinex/Claritin; Prilosec/Nexium)
- Review Rx-to-OTC use applications

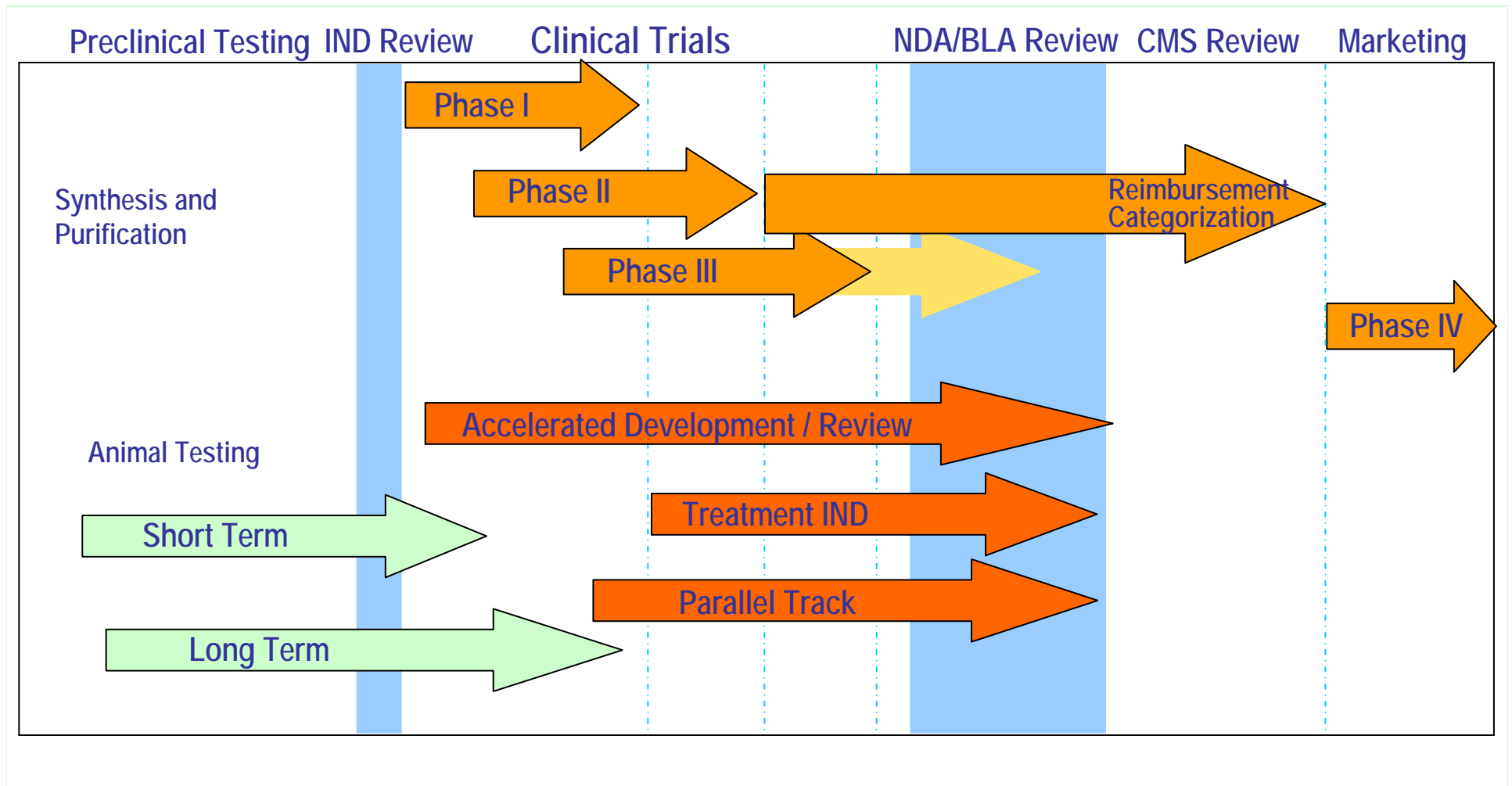
Evaluating the Target's Lifecycle Management

- Assess potential economic impact of any NDAs, BLAs, 505(b)(2) applications or ANDAs filed by others
- Review any FTC/private actions regarding the target's lifecycle management activities
- Review any corporate integrity agreements affecting lifecycle management
- Monitor development of a potential regulatory pathway for approval of generic biologics/biosimilars in the U.S. and any EU approvals
 - *See Sandoz, Inc. v Leavitt (D.D.C. 2006)*

3. Evaluating the Target's Healthcare Reimbursement Status

- Review product's reimbursement status under Medicare, Medicaid, private healthcare insurer programs
- Review history of interactions with Centers for Medicare and Medicaid Services (CMS)
 - Review any discussions by the target at investigational stage with CMS on therapeutic reimbursement category and coverage of the product

Evaluating the Target's Healthcare Reimbursement Status



Evaluating the Target's Healthcare Reimbursement Status

- Review compliance with healthcare pricing, marketing, distribution
 - *OIG, Compliance Program Guidance for Pharmaceutical Manufacturers (April 2003)*
 - *Pharmaceutical Research and Manufacturers of America (PhRMA), Code on Interactions with Healthcare Professionals (July 2002)*
- Review any investigations/enforcement actions regarding pricing/marketing/off-label promotion
 - *Anti-kickback statute*
 - *False Claims Act*
 - *State marketing disclosure laws*

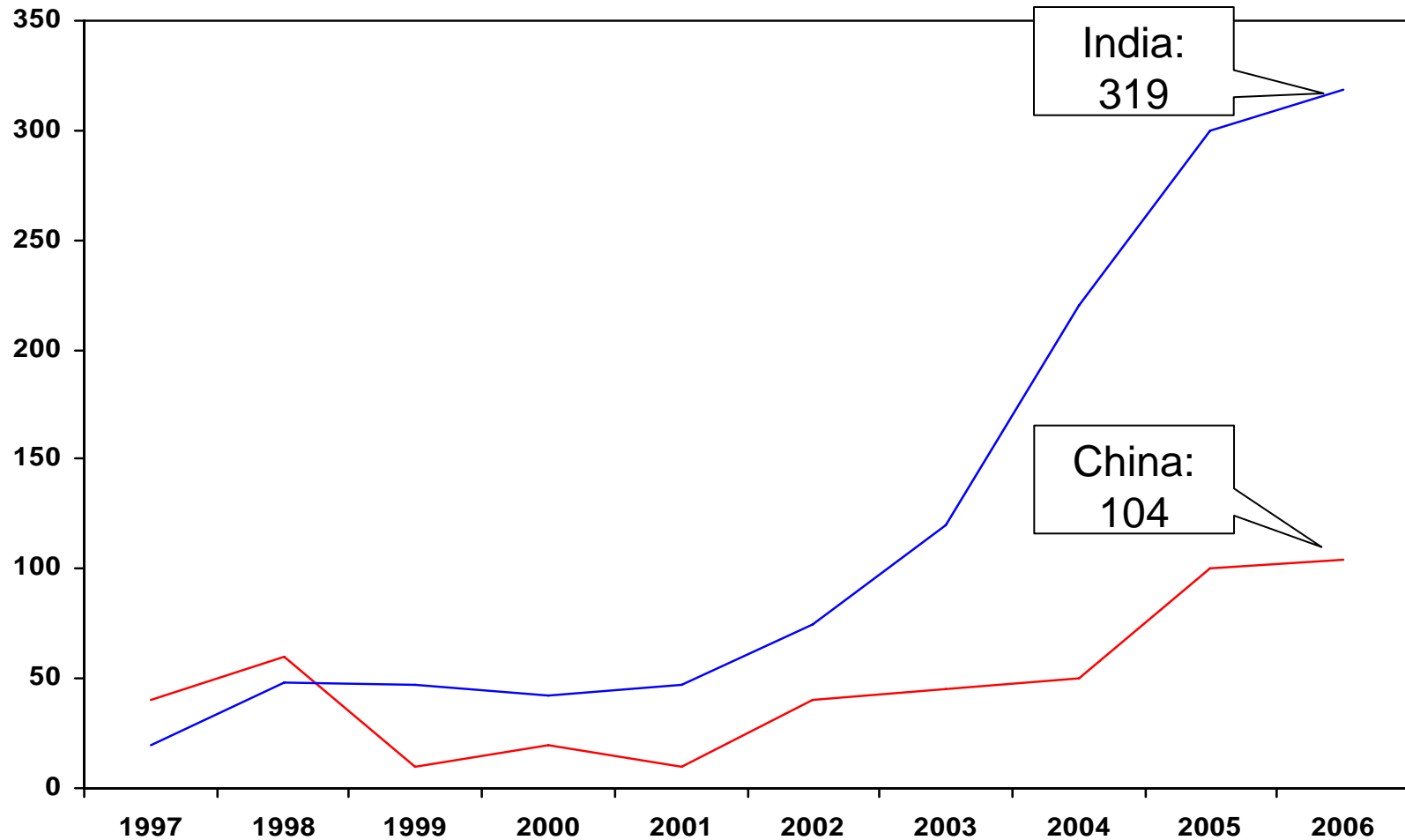
Evaluating the Target's Healthcare Reimbursement Status

- Assess whether comparative effectiveness or cost effectiveness trials are components of target's clinical trials
 - Increasing importance of inclusion of pharmacoeconomics considerations at clinical trials stage
 - 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)
 - Review any assessments by the U.K.'s National Institute for Healthcare and Clinical Excellence

4. *Drafting an Agreement Incorporating Current Regulatory Concerns*

- Manufacturing quality issues
 - Review outsourcing of clinical trials/manufacturing
 - Up to 65 percent of clinical trials expected to be done outside the US (Tufts University Center for the Study of Drug Development, Jan. 2007)
 - Increasing movement to outsource manufacturing
 - Inclusion of rights to monitor outsourcing partners (CRO/co-development partners/third-party manufacturers)
 - Inclusion of notification/related rights regarding FDA inspections/manufacturing concerns

Filings to the FDA to sell active pharmaceutical ingredients



Drafting an Agreement Incorporating Current Regulatory Concerns

- Labeling and promotion issues
 - Inclusion of rights to assess proposed labeling changes/safety and contraindications
 - Rights to review AERs/pharmacovigilance reports
- Marketing/fraud and abuse
 - Rights to review off-label promotion
 - Monitor any government investigations/litigation regarding fraud and abuse

Drafting an Agreement Incorporating Emerging Regulatory Concerns

- Phase IV post-approval studies obligations
 - Rights to review/control Phase IV negotiations with FDA
 - Rights to monitor Phase IV studies
- Reimbursement/pricing
 - Rights to review/monitor comparative/cost effectiveness studies
 - Rights to review/monitor interactions with CMS and reimbursement/coverage strategy decisions
 - Royalty adjustments in the event of adoption of a regulatory approval pathway for generic biologics/biosimilars

5. Considering the Impact of the FDA Amendments Act of 2007

- Food and Drug Administration Amendments Act of 2007 (H.R.3580) – signed by the President (Sept. 27, 2007)
 - Provides FDA with authority to order post-approval clinical studies or trials
 - Provides FDA with authority to require a drug or biologic to have a Risk Evaluation and Mitigation Strategy (REMS) if serious risks are found
 - Requires manufacturers to post certain information on the NIH clinicaltrials.gov data registry, expanded to include efficacy and post-approval trials
 - Requires the FDA create a post-market surveillance system
 - Provides FDA with authority to require safety labeling changes
 - 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 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.”

6. Potential Adverse Effects of Regulatory Issues on Valuation

- Effects on payors of FDA safety concerns
- 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 for 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

Potential Adverse Effects of Regulatory Issues on Valuation

- Adoption of mirror restrictions on coverage and reimbursement by private insurers
 - One private insurer, Aetna, altered its coverage to reflect the restrictions imposed by CMS on ESAs
- Potential for restrictions by other government purchasers
 - Decision by Department of Veterans Affairs (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

Potential Adverse Effects of Regulatory Issues on Valuation

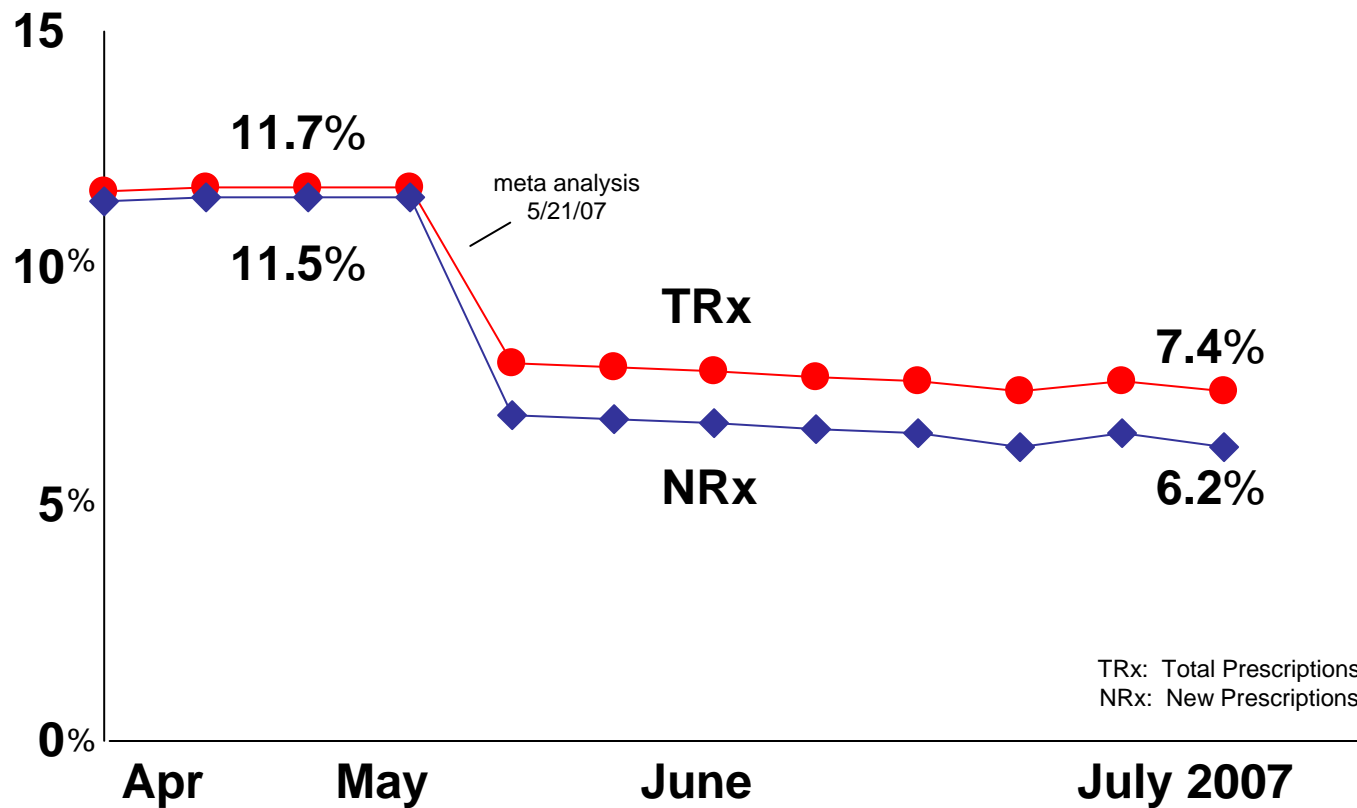
Effect of FDA safety actions on market valuations of selected drug products and companies

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, 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)

Potential Effects of Regulatory Issues on Valuation

- 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 cost/comparative effectiveness studies can be expected to lead to reductions in coverage and reimbursement levels by the government and private payors

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