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deskbook

Emerging Life Sciences Companies

second edition

Chapter 30

Issues That Must Be Addressed in a Life Sciences M&A

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ISSUES THAT MUST BE ADDRESSED IN A LIFE SCIENCES M&A

As demonstrated in the previous chapter, there are a number of unique challenges that a life sciences company faces in a merger or acquisition. In addition, a life sciences company like yours will encounter unique items that must be addressed during diligence as well as when negotiating and drafting a merger or acquisition agreement. In particular, the scope of regulatory issues has changed in life sciences mergers and acquisitions. There is increased scope and significance of FDA regulatory issues/safety concerns; new pricing/reimbursement issues; and an expansion of the number of, and competition for, life science companies. The following outline sets forth many of such issues.

Assessing the Target Company's FDA Regulatory Status

A. Investigational products

1. Current status—preclinical studies; Phase I, II, or III studies; and pending marketing applications

    a. Review recent public statements by the target company

    b. Review IND documents and/or pending marketing applications (NDA/BLA)

2. Compliance

    a. Inspections of CRO or clinical site/investigator

    b. Clinical holds

    c. IRB approval/informed consents

    d. IND reporting requirements

    e. Chemistry, manufacturing, controls (CMC) package

    f. Protocol amendments

    g. Financial disclosure

    h. No debarred individuals/entities

    i. Preapproval promotion

B. Marketed products

1. Review of scope of approval or other regulatory basis for marketing
2. Determine basis of marketing (NDA, BLA, grandfathered drugs)
3. Scope of indications: contraindications; limited patient population; other express limitations
4. Review any RiskMAP imposed (see FDA guidance on risk management programs (March 2005))

C. Manufacturing compliance

1. Review audits, inspection history (FD 483s), state licensure to determine compliance with Good Manufacturing Practice (GMP) regulations
2. If contract manufacturing, review contract, complaints, audits, master files, FDA inspections history
3. Review compliance for both finished pharmaceuticals and active pharmaceutical ingredients (APIs)
4. Review manufacturing costs/API availability

D. Marketing/Promotion compliance

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

E. Distribution compliance

1. Compliance with Prescription Drug Marketing Act (PDMA)
2. Review FDA inspection/compliance history
3. Review compliance with state licensure requirements for distribution facilities
4. Review Drug Enforcement Administration (DEA) regulations to determine compliance for controlled substances

Reviewing the Target Company's Drug Safety Profile

A. Increasing scrutiny of drug safety

B. Review product liability litigation

C. Review of study data

   1. Preclinical studies

   2. IND studies

   3. Phase IV postmarketing studies

   4. Comparative safety/efficacy studies

D. Other items to review for the target company's drug safety profile

   1. Compliance with Good Laboratory Practices (GLPs) and Good Clinical Practices (GCPs)

   2. Compliance with regulations on Care and Use of Laboratory Animals (21 C.F.R. § 58.90)

   3. Compliance with clinical monitoring of studies requirements

   4. Review of any clinical trials conducted in foreign countries

   5. Review Adverse Experience Reports (AERs), pharmacovigilance data, and complaints

   6. Review FDA clinical holds/studies halted voluntarily/recalls

   7. Review FDA correspondence/meeting minutes regarding safety issues/studies

   8. For investigational products, review FDA requests for additional data

   9. Review any RiskMAPs

   10. Anticipate any new studies

Evaluating the Target Company's Lifecycle Management

A. Review patent status

B. Review patent term extension status (potential up to five years)

C. Review five-year market exclusivity for new chemical entities (NCEs) under Hatch-Waxman Amendments

D. Review three-year market exclusivity for new indications/applications under Hatch-Waxman Amendments (e.g., OTC use)

E. Review Orphan Drug exclusivity (seven years)

F. Review pediatric exclusivity (six months)

G. Review generic drug 180-day exclusivity and authorized generic filings

H. Review product extension filings (new dosages/indications/routes of administration)

I. Review follow-on products

J. Assess potential economic impact of any NDAs, 505(b)(2) applications, or ANDAs filed by others

K. Review any FTC/private actions regarding the target's lifecycle management activities

L. Review any corporate integrity agreements affecting lifecycle management

M. Monitor development of a potential regulatory pathway for approval of generic biologics

Evaluating the Target Company's Healthcare Reimbursement Status

A. Increasing importance of reimbursement issues

1. Effect on target product/company valuation

2. Increasing impact of payor considerations on drug development/acquisition decisions

B. Review product's reimbursement status under Medicare, Medicaid, private healthcare insurer programs

C. Review history of interactions with Center for Medicare and Medicaid Services (CMS) and any discussions by the target company at investigational stage with CMS on therapeutic reimbursement category and coverage of the product

D. Review compliance with healthcare pricing, marketing, distribution

1. OIG, *Compliance Program Guidance for Pharmaceutical Manufacturers* (April 2003)

2. Pharmaceutical Research and Manufacturers of America (PhRMA), *Code on Interactions with Healthcare Professionals* (July 2002)

E. Review any investigations/enforcement actions regarding pricing/marketing/off-label promotion

1. Antikickback statute

2. False Claims Act

3. State marketing disclosure laws

F. Assess whether comparative effectiveness or cost-effectiveness trials are components of target company's clinical trials

1. Increasing importance of inclusion of pharmacoeconomics considerations at clinical trials stage

2. First comparative effectiveness trial of two pioneer drugs, by National Institutes of Health, announced February 2007 (see comparative trial of two Genentech drugs [Lucentis—$2,000/dose and Avastin—$40/dose])

3. Review any assessments by the UK's National Institute for Healthcare and Clinical Excellence

Assessing the Potential for Antitrust Issues/Reportability

A. Assessing reportability/valuation

1. Asset acquisitions

2. Collaboration agreements

B. Numerous issues regarding exclusivity and valuation of collaboration agreements

1. Field of use/geographic territory limitations

2. March-in or termination rights

3. Transfer of manufacturing rights

4. Combination product rights

5. Estimation of fair market value/contingency payments

C. Assessment of worldwide reportability

D. Substantive antitrust analysis

1. Product market definition

a. Key factors: therapeutic substitutability; mechanism of action; AB rating

2. "Innovation market" analysis—crucial in life sciences mergers and acquisitions

a. Assessment of product development pipelines of parties and others/ competitor entry

b. *See In re Genzyme Corp.* (FTC press release January 13, 2004); Statement of FTC Chairman T. Muris regarding closing of investigation of Genzyme acquisition of Novazyme (January 14, 2004)

c. *See* FTC/Department of Justice Division, *Commentary on the Horizontal Merger Guidelines* (March 2006)

3. Assessment of any FTC/DOJ investigation of the target company's lifecycle management activities

a. Hatch-Waxman Act litigation and settlements; citizen petitions to FDA; introduction of authorized generics

4. Joint venture analysis

a. FTC/DOJ Antitrust Division, *Antitrust Guidelines for Collaborations Among Competitors* (April 2000)

Drafting an Agreement Incorporating Current Regulatory Concerns

A. Manufacturing quality

1. Ensure coverage of outsourcing
2. Inclusion of rights to monitor outsourcing partners (CRO/co-development partners/third-party manufacturers)
3. Inclusion of notification/related rights regarding FDA inspections/ manufacturing concerns

B. Labeling and promotion

1. Inclusion of rights to assess proposed labeling changes/safety and contraindications
2. Rights to review AERs/pharmacovigilance reports

C. Reimbursement/pricing

1. Rights to review/monitor comparative/cost-effectiveness studies
2. Rights to review/monitor interactions with CMS and reimbursement/ coverage strategy
3. Royalty reductions for introduction of generic competition (including potential generic biologics) and competitive products

D. Marketing/fraud and abuse

1. Rights to review marketing/detail force materials
2. Rights to review off-label promotion
3. Monitor any government investigations/litigation regarding fraud and abuse

E. Phase IV postapproval obligations

1. Rights to review/control Phase IV negotiations with FDA
2. Rights to monitor Phase IV studies