

Chapter 21

FDA DUE DILIGENCE FOR PHARMACEUTICALS AND BIOLOGICS PRODUCTS

When looking to partner with another company through an in-license transaction or collaboration agreement, or when seeking to acquire a product outright from another company, you should undertake due diligence on a number of FDA items before entering into such a transaction.

Summarize Scope of FDA Due Diligence

- A. Identify all intellectual property with a complete list of products currently marketed and under development.
- B. Identify and list the regulatory status of products under development (including with respect to orphan, pediatric, fast track, etc.).
- C. List all marketing applications filed and/or approvals received in the United States and foreign countries.

Drug Master Files

- A. List any drug master files (DMFs) that the company has filed.
- B. Catalog any deficiency letters for any DMF.
- C. Catalog the annual reports updating each of the DMFs.
- D. Identify the companies, if any, authorized to reference each of the DMFs.
- E. Request all FDA correspondence concerning any DMF.

Investigational Research

- A. Determine whether appropriate and adequate in vitro and in vivo preclinical testing for approved/pending products has been conducted by the company or contract laboratories on the company's behalf.
 - 1. Determine whether the preclinical studies were conducted by the company or contract laboratories in accordance with FDA current Good Laboratory Practices (GLPs) regulations.
 - 2. Has the company or its contract laboratories ever been cited for failure to comply with GLPs? Has data in support of a product application ever been audited or disqualified because of noncompliance?

3. Determine if the laboratory facility is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care.
 4. Document compliance with regulations on Care and Use of Laboratory Animals (21 C.F.R. § 58.90).
 5. Document compliance with Good Clinical Practice (GCP) regulations.
 6. Obtain assurances that there has been no use of services of any person who has been debarred, under 21 U.S.C. § 335a(a) or (b), in any capacity for conduct relating to the development or approval of any drug product. Confirm that neither the company nor any of its officers or employees has been convicted of a felony under federal law for conduct relating to the development or approval of any drug product, new drug application (NDA), abbreviated new drug application (ANDA), Product License Application (PLA), Establishment License Application (ELA), or Biologics License Application (BLA).
- B. Review all Investigational New Drug (IND) applications for products being developed by the company for status and compliance with FDA regulations. Request all FDA correspondence concerning any IND.
1. Provide the IND number for each application.
 - a. Who is the sponsor of each IND, e.g., the company or an investigator-sponsored trial (IST)?
 - b. Has appropriate Institutional Review Board (IRB) approval of the clinical trials been obtained and maintained (e.g., for changes to the clinical trial protocol)?
 - c. Have investigators all signed appropriate investigator statements (FDA Form 1572) and research agreements? Has there been appropriate review of investigators with respect to FDA compliance, including financial disclosures? Have adequate records and reports of the clinical trials been maintained? Have adverse experience reports been kept and accurately reported?
 - d. Review the informed consent forms for all clinical trials. Do they comply with 21 C.F.R. Part 50? Do the forms' descriptions of "any reasonably foreseeable risks" include appropriate references to risks presented by the investigational products?
 - e. Have there been annual reports filed in connection with all INDs? If so, provide a list and copies.
 - f. Have any of the protocols in the ongoing investigations ever been amended, and, if so, were the amended protocols submitted to FDA?
 2. Have any deficiency letters been issued from FDA relating to the INDs? If so, what was the outcome? Review all correspondence to and from FDA on this issue. Note how the issues were resolved.

3. Has any clinical research been terminated, put on clinical hold, or voluntarily withdrawn? If so, why?
 4. Are any of the INDs considered inactive? How long have they been inactive and why?
 5. Does the company have a treatment IND or an application for a treatment IND? If so, review all such applications. Have adequate reports and records been maintained under such treatment INDs, including any adverse experience reports?
 6. Has the company ever had its clinical investigation records audited by FDA? What was the outcome? Have any clinical sites ever been inspected and, if so, what was the outcome?
 7. Have there been any pre-IND or other clinical research phase meetings with FDA relating to the products under development? Review and summarize minutes of same. Did the company receive formal communications from FDA for clinical trials?
 8. Has the company submitted a Special Protocol Assessment to FDA for any protocol?
 9. Are any clinical trials being conducted in foreign countries?
 10. Is the company aware of any similar research being undertaken by another entity or entities on the same or substantially similar products?
 11. Besides indication and route of administration, what are the distinctions between the company's products under development and commercially available products?
 12. Is the company acting as the monitor of its investigations or has it selected other monitors? If the latter, who are the monitors for each investigation?
 13. Is clinical monitoring being conducted in accordance with FDA regulation 21 C.F.R. § 312.56 and FDA guidelines on clinical monitoring?
 14. Can the company confirm that it has not promoted or commercialized any of its investigational drugs? Is there any preapproval promotion evident? If so, does it comport with FDA's regulatory restrictions on such promotions?
 15. Does the company charge patients for any of its investigational drugs, and, if so, did it obtain FDA approval? Does the company submit insurance for its coverage of its investigational products or other services required as a result of the trial?
 16. Can the company certify that all clinical data obtained to date is true and accurate?
 17. Has an IND safety report ever been filed for any of the products under development pursuant to 21 C.F.R. § 312.32?
 18. Are the investigational products labeled in accordance with 21 C.F.R. § 312.6?
 19. Have applicable clinical studies been posted at clinicaltrials.gov?
- C. Determine whether any FDA Advisory Review Committees have ever rejected studies conducted or supervised by the company, or found such studies to be insufficient.

If so, determine on what basis studies were rejected, found insufficient, or required to be supplemented or redone, and outcome of same.

- D. Determine whether the company has ever been investigated for data fraud by FDA, the Department of Justice, or any other governmental entity. If so, obtain relevant documentation related thereto.
- E. Determine whether the company conducts or supervises clinical studies in foreign locations for purposes of U.S. approval.
- F. Has accelerated (fast track) FDA review, orphan drug, or pediatric status been sought for any of the company's products? Provide any correspondence to/from FDA documenting such requests and any response.

Marketing Applications

- A. Determine the status of all pending and approved U.S. and foreign marketing applications for drugs and biologics, including NDAs, ANDAs, PLAs, BLAs, and foreign equivalents. Request all correspondence with FDA or relevant foreign governmental agency concerning any U.S. or foreign marketing application.
- B. Confirm the company has complied with all registrations, authorizations, filings, and listings associated with pending and approved U.S. and foreign marketing applications for drugs and biologics, including but not limited to those related to establishment registration, product listing, and patent listings, and foreign equivalents.
- C. Determine whether all payments have been made under the Prescription Drug User Fee Act, as amended, for marketing applications.
- D. Confirm the company has complied with all annual and any other applicable reporting requirements for all registrations, authorizations, filings, and listings associated with pending and approved U.S. and foreign marketing applications for drugs and biologics.
- E. Confirm the company has complied with any postmarket/Phase IV study obligations.

Good Manufacturing Practice Considerations

- A. Manufacturing Processes
 - 1. To what extent does the company manufacture its products (either approved or for use in clinical trials)? Does the company use a contract manufacturer for all or part of the manufacturing process(es)?
 - 2. If a contract manufacturer is used for all or part of the manufacturing process(es), review a copy of the agreement concerning manufacture of the products as to its accordance with FDA good manufacturing practices (GMPs) and specifications provided by the company.
 - 3. To the extent that the company manufactures its products, are its manufacturing facilities in compliance with GMP requirements?
 - 4. Has the company or its contract manufacturing facilities been inspected by FDA?

When? Were deficiencies identified? How were they resolved? Determine and summarize the company's compliance history with GMPs. Review copies of all FDA correspondence relating to GMPs, compliance matters, establishment inspection reports, FDA Form 483s, Warning Letters, and all company responses to such correspondence and forms.

5. Determine if the company has a GMP manual. Review the company's GMP manual or standard operating procedures (SOPs) to ensure that they contain an adequate description of key quality assurance activities required by FDA (i.e., procedures with respect to organization of personnel, buildings and facilities, equipment, production and process controls, packaging and labeling controls, holding and distribution, records and reports, and returned and salvaged drug products).
 6. Identify and confirm current FDA ELAs for each of the company's manufacturing facilities, if required.
 7. Request all FDA correspondence concerning GMP compliance.
- B. Adverse Experience Reports/Complaint Procedures (as appropriate)
1. Review the company's adverse experience reports (AERs) and GMP complaints. Do any complaints appear not to be resolved?
 2. Confirm that any complaints involving product specification failures have been evaluated, reviewed, and investigated by the company, consistent with GMP requirements.
 3. Determine whether files have been established for AERs and GMP complaints. Determine whether the company has received any complaints relating to serious injuries or deaths. How have these complaints, if any, been resolved? Have they been properly reported to FDA?
 4. Determine whether periodic complaint trend analyses/pharmacovigilance were conducted, and, if so, review the analyses to identify the frequency and severity of complaints.
- C. Determine whether there are any product liability suits past, pending, or threatened against the company with respect to its products. If any such suits are pending or threatened, such files should be reviewed by litigation counsel.

Marketing and Promotion

- A. Review the company's promotional and marketing materials, press releases, labeling, brochures, abstracts, or other statements for all drug and biologic products. Has the company ever promoted its products for unapproved or off-label uses? Request all correspondence with FDA concerning the company's promotion and marketing practices, including any Untitled Letters, Warning Letters, Cyber Letters or other correspondence from DDMAC.
- B. Review detail force/MSLs training/SOPs/promotional pieces; review any

counter-detailing pieces.

- C. Are any products covered by restricted distribution programs (RiskMAPs) or a Risk Evaluation and Mitigation Strategy (REMS)?
- D. Does the company manufacture and market authorized generics?
- E. Has the company engaged in cost-effectiveness or comparative effectiveness promotional activities?
- F. Does the company undertake direct-to-consumer (DTC) advertising? If so, has the company sought FDA advisory review for its DTC television advertising?
- G. Does the company engage in Internet and new media promotion, such as e-details or podcasts?
- H. Is the company aware of any 505(b)(2) or ANDAs filed with respect to its products?
- I. Is the company aware of any applications for biosimilars/generic biologics filed internationally with respect to its products?

Over-the-Counter Drugs

- A. Does the company manufacture and market over-the-counter (OTC) drugs?
- B. Determine the basis upon which OTC drugs are marketed (e.g., under a final or proposed OTC drug monograph; Rx-to-OTC use application approved by FDA; generally recognized as safe and effective (GRASE) status; grandfathered status).
- C. Determine whether the company's labeling and advertising claims are consistent with applicable final or proposed monographs.
- D. Determine whether the company's marketing and sales of OTC drugs have ever been the subject of complaints or challenges (e.g., by FDA, the Federal Trade Commission, state attorneys general, competitors, the National Advertising Division of the Council of Better Business Bureaus). If so, how were the complaints resolved?

FDA Regulatory Enforcement/Oversight

- A. Determine whether any product has ever been the subject of a Regulatory Letter, Notice of Adverse Findings, Notice of Violation, Warning Letter, or any other type of correspondence in which FDA or a state governmental authority stated or suggested that the company violated laws, regulations, or policies. Request copies of such correspondence.
- B. Determine how the company resolved such allegations. Are the investigations closed or terminated? Review all documents resulting from such investigations (e.g., consent orders, corporate integrity agreements, voluntary compliance programs).
- C. Determine the company's process for conducting due diligence of employees and contractors concerning debarment or exclusion status. Document that there has been no use of services of any person who has been debarred, under 21 U.S.C. § 335a(a) or

(b), or excluded in any capacity for conduct relating to the development or approval of any product.

- D. Has any foreign governmental authority taken any adverse action regarding any product under development or any substantially similar product?
- E. Has the company ever received any compliance correspondence relating to products under development from a foreign governmental entity with jurisdiction over pharmaceuticals?