DuaneMorris

Legal Aspects of Outsourcing

Outsourcing 101
Joint OCRA/SDRAN Conference
November 19, 2014

Michael A. Swit, Esq.
Special Counsel, FDA Law Practice

Standard Disclaimers

- Views expressed here are solely mine and do not reflect those of my firm or any of its clients.
- This presentation supports an oral briefing and should not be relied upon solely on its own to support any conclusion of law or fact.
- These slides are intended to provide general educational information and are not intended to convey legal advice.

What I Will Cover

- Key Contract Clauses
- FDA and Quality Agreements
- Due Diligence
- Why Legal Issues Are Important … *aka* … ***What Can Go Wrong***
- Unique Issues in Outsourcing

Key Contract Clauses

Contract Clauses …

- **Buyer's right to audit vendor or contract partner (and vendor's key suppliers)**
  - without notice
  - at any reasonable time during operations
  - vendor to cooperate fully with audit
  - access to records and personnel to be spelled out
- **Why audit?**
  - Right is a check on partner sliding toward non-compliance
  - Good sense – and required by FDA regs (at least on devices)

Contract Clauses …

- **Advance *notice of changes* in vendor's processing – so …**
  - Buyer can assess what regulatory action it must take to keep its approval/submission current
  - Buyer can assess if change might change nature of product
    - e.g., carbamazepine – change in synthesis led to different crystalline structure – met spec, but triggered an unexpected adverse event – API maker did not tell finished dosage form company – massive recall

Contract Clauses …

- **Vendor to cooperate, at no *[or $___]* additional expense, with Buyer's needs to take action to continue to comply with FDA requirements (e.g., vendor to provide data to support filing of supplements to make changes to approved applications)**
  - Another Example – sell off all the rights to a product, but are you stuck having to continue stability data on what was already made? If so:
    - Did your price include such items?
    - Do your personnel understand they will need to do this?

Contract Clauses …

- **Vendor's relations with FDA …**
  - Provide copies of *483's, EIRs*
  - Prompt notice to buyer of *initiation of FDA inspections*
  - Prompt transmission/notice to buyer of any *FDA regulatory correspondence or other regulatory action*
  - Right of partner to have a representative at other partner during an FDA inspection

Contract Clauses …

- **Timely *notice of other problems* encountered by vendor in its manufacturing process**
  - *Example*: problems in making similar products for others – duty to notify you
- **Timely *notice to buyer of any adverse reactions or complaints* reported to vendor**
  - Caveat: define "timely"
    - ***Case study*** – Lilly/Icos Jt. Venture on Cialis – approval delayed about a year due to quality problems at Lilly plant
- ***Recalls* -- duty of responsible partner to cooperate with recalls initiated by other partner (if applicable)**
  - clauses on who pays damages

Contract Clauses …

- **Active Pharmaceutical Ingredient (API) Sourcing**
  - DMF Maintenance –
    - Notice of updates
    - Duty to file at FDA
  - Specify GMP level compliance (U.S. v. EU v. WHO v. ??)
  - IP Compliance – that they are not violating any process patents
  - How DMF file will be updated and who bears the burden of cost to ensure done correctly; audit right on DMF changes?
- **Other ingredients or components**
  - specifications (e.g., USP)
  - testing – state where done (whose lab)

Contract Clauses …

- **Pre-approval inspections**
  - Notice to Buyer when scheduled
  - Handling
- **Ownership of formulations --**
- **Allocation of NDA related duties**
  - Preparing batch records
  - Preparing labeling
- **IND Formulations –** type of equipment and extent of GMP controls applied (varies by phase)
- **Ensuring scale-up and validation done properly**
- **Bottom line – want it done, put it in the contract**

Due Diligence

Due Diligence Structure

- **Focus on areas of greatest criticality – each due diligence will be unique**
- **Essential to use qualified Quality professionals to conduct due diligence**
  - U.S. FDA expertise
  - E.U. and other foreign agencies, as applicable
    - ***Fallacy #1*** – if it's good enough for FDA, the rest of the world will accept it
  - Don't rely on a paper review – for key vendors, you have to go audit them and fully qualify them

History of Compliance

- **Does the vendor have a history of issues with FDA relating to quality?**
  - Inspections – 483s
  - Warning Letters
  - Official action -- consent decrees, injunctions, seizures, criminal prosecutions
- **Assess company responses**
  - Did they hear FDA's "D.R.U.M.?"
    - Direct, Related, Universal, Monitoring and Management
  - Any continued duties from prior inspections, Warning Letters?

FDA Inspectional History

- **When did FDA last inspect?**
- **How many inspections over five years?**
  - For cause (e.g., recalls, complaints, AEs)
  - Routine
- **What is relationship with FDA District Office?**
- **If 483s, are responses great, good or "oh no"**

Internal Audits

- **Does firm have an internal audit procedure?**
  - Ensure it was followed
  - Review reports
- **Has the firm had audits commissioned outside experts to audit its operations?**
- **Has the firm been the subject of a third-party audit (e.g., a partner or customer)?**

Diligence Techniques

- **Review FDA "correspondence"**
  - 483's
    - Company responses
  - Warning letters
    - Company responses
- **Assure yourself that problems have been corrected**
  - If necessary, audit the facility to confirm (at least selected key issues), unless they share an FDA close out letter with you.

Diligence Techniques …

- **Verify if any litigation exists that raises quality concerns (e.g., personal injury suits alleging injury or illness from a defectively-made drug)**
  - Ask if any exist.
  - Review complaints/answers if any exist for allegations of defective operational practices that might have escaped FDA's eyes.
  - Review CAPAs.

FDA and Quality Agreements

2013 Draft Guidance on Quality Agreements

- ***Contract Manufacturing Arrangements for Drugs: Quality Agreements*** – May 2013 ***[Hot Link]***
  - Must delineate who is responsible for each activity, although you can not contract away liability under the Act
    - ultimately, the "***owner***" is still responsible for compliance – i.e., the firm that actually markets the product
    - similar duty – in the IND regulations for delegating to a CRO
  - While only technically applicable to drugs and biologics, contains guidance that device firms also should emulate

Quality Unit Activities

- **Final product release and the release of a product for the operations performed at the Contracted Facility**
  - Owner – must perform final release, although guidance is silent on how done
- **Communication plan between the Owner and Contracted Facility**
- **Procedures for the Owner's evaluation and audit of the Contracted Facility's operations**
- **The parties' expectations for regulatory inspections and obligations for reporting inspection findings.**

Facilities and Equipment Activities

- Detail the site at which manufacturing activities will be performed
- Validation, qualification and maintenance activities
- Other facilities and equipment maintenance.

Materials Management Activities

- Setting specifications for raw materials and conducting sampling/testing
- Inventory management, quarantine and prevention of mix-ups and cross-contaminations
- Allocation of responsibility for storage under labeled conditions.

Product-Specific Terms

- Product/component specifications
- Defined manufacturing operations (*e.g.*, batch numbering, expiration/retest dating, lot disposition, etc.)
- Process validation (design, qualification and ongoing validation)
- The Owner's personnel with authorization to be in the Contracted Facility

Laboratory Controls

- **Controls over sampling and testing samples**
- **Qualification, calibration and maintenance of laboratory equipment**
  - responsibility should rest with the Contracted Facility, and
  - Owner should audit these activities.)
- **Laboratory investigations, including deviations, discrepancies, failures and out-of-specification laboratory results**
- **Detail requirements for CoA contents (e.g., state with precision where done, what tests performed, etc.)**

Documentation

- Procedures for the Owner to review and approve documents (*i.e.*, Standard Operating Procedures, laboratory records, etc.)
- Accessibility of cGMP-related documents
- Maintenance of cGMP-related documents under a certification or controlled copy procedure
- If applicable, processes to maintain the integrity and reliability of electronic records.

Change Control

- **Parties must detail:**
  - when the Contracted Facility must notify the Owner of any changes in the facility's operations or processes (*e.g.*, process capability analysis, customer complaints, recalls, or new or revised product claims), and
  - Which changes require, or do not require, Owner review and approval.

Why Legal Issues Are Important … *aka* …

What Can Go Wrong

What Can Go Wrong

- **Poor Suppliers May Delay or Void an Approval**
  - Active Pharmaceutical Ingredient ("API") Supplier
    - Sponsor's application will not be approved if deficiency at API maker
    - ***Special tactics/concerns:***
      - be extremely careful with first-time suppliers
      - special concern -- if never used before, FDA foreign inspection may delay approval process as well
  - Inactive Ingredients or components issues
    - contamination can lead to recalls
      - Sterling Gelatin – inexpensive ingredient triggers major recall

What Can Go Wrong …

- **Poor Suppliers May Delay or Void an Approval …**
  - Contract Manufacturers
    - must be GMP compliant or FDA approval can be refused
    - ***Special tactics/concerns***
      - tied directly into your application -- their changes will trigger a regulatory duty that may require an FDA filing/approval
      - may be high volume/low margin producers -- pressure on production may lead to errors
    - Example – Ranbaxy – FDA just rescinded two tentative ANDA approvals

Unique Issues in Outsourcing

Unique Issues

- ***Back-up Manufacturing Plant***
  - **When needed:** whenever manufacturing is contracted out for IND or approved
  - ***Example:*** Lilly – 7/18/02 public announcement on 2nd Quarter results and plant problems not being cured until 2003
  - **What clause says:** lets non-mfg. party seek a backup contractor under appropriate circumstances (e.g., Lilly had GMP problems holding up NDA approvals)

Unique Issues …

- **Who Owns the Data?**
  - **When needed:** whenever studies of any sort are farmed out
  - ***Example: Client has major study done at University; contract is ambiguous on who controls the data, although clear client can use in FDA product approval filing***
  - **What clause says:** makes clear who owns both raw data and results and the right to authorize publications and references

Unique Issues …

- **Right to Copies of Data**
  - **When needed:** when laboratory analyses are done by a third party vendor
    - What do you do if the vendor goes bankrupt?
  - ***Example:*** Oread – Kansas lab went bankrupt; closed its doors. All lab results stored in a cavern.
  - **What clause says:** grants buyer the right to have copies of documents (or originals) and lab (or trustee in bankruptcy) can not destroy
    - but, you will need to agree to pay for costs because won't be any money for bankruptcy trustee to handle

Questions?

- ***Call, e-mail or fax:***

Michael A. Swit, Esq.
Special Counsel, FDA Practice
Duane Morris LLP
San Diego, California
direct: 619-744-2215
fax: 619-923-2648
maswit@duanemorris.com

- ***Follow me on:***
  - LinkedIn: http://www.linkedin.com/in/michaelswit
  - Twitter: https://twitter.com/FDACounsel

About Your Speaker

***Michael A. Swit, Esq.*, is a Special Counsel in the San Diego office of the international law firm, Duane Morris, LLP, where he focuses his practice on solving FDA legal challenges faced by highly-regulated pharmaceutical and medical device companies. Before joining Duane Morris in March 2012, Swit served for seven years as a vice president at The Weinberg Group Inc., a preeminent scientific and regulatory consulting firm in the Life Sciences. His expertise includes product development, compliance and enforcement, recalls and crisis management, submissions and related traditional FDA regulatory activities, labeling and advertising, and clinical research efforts for all types of life sciences companies, with a particular emphasis on drugs, biologics and therapeutic biotech products. Mr. Swit has been addressing vital FDA legal and regulatory issues since 1984, both in private practice with McKenna & Cuneo and Heller Ehrman, and as vice president, general counsel and secretary of Par Pharmaceutical, a top public generic and specialty drug firm. He also was, from 1994 to 1998, CEO of *FDANews.com,* a premier publisher of regulatory newsletters and other specialty information products for FDA-regulated firms. He has taught and written on many topics relating to FDA regulation and associated commercial activities and is a past member of the *Food & Drug Law Journal* Editorial Board. He earned his A.B., *magna cum laude*, with high honors in history, at Bowdoin College, and his law degree at Emory University.**