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Advanced Licensing Agreements 2017

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Key Considerations in License Agreements Specific to the Life Sciences Industry

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I. KEY CONSIDERATIONS IN LICENSE AGREEMENTS SPECIFIC TO THE LIFE SCIENCES INDUSTRY

A. Importance of Alliances/Licensing in Biotech/Pharma Industry

1. The value of licensing deals in the pharmaceutical industry is large and getting larger: in 2015 it increased by 37.1% to $46.2 billion (Source: GlobalData report, The PharmaLetter, July 17, 2016). According to Thomas Reuters, there were 955 publicly announced licenses and joint ventures in the life sciences industry in 2015 with a combined value of $65.2 billion.

2. The greatest number of deals, and the biggest deals in terms of reported values, continued to come from the oncology therapeutic area, reflecting the size of the market opportunity, the level of unmet need, and the emergence of exciting new approaches in immuno-oncology and gene therapy, among others. 35% of all licensing deals in 2015 were in oncology and almost half of the 32 biggest deals in 2015 were in oncology, which also represented the 3 biggest deals and 5 of the 6 biggest in terms of reported up-front payments. Other notable therapeutic areas include CNS and diabetes. (Source: Thompson Reuters; FirstWord Pharma, Dec. 23, 2015)

3. More than half of biotech/ pharma licensing deals done in 2015 were at the preclinical or early (Phase I) clinical stage. Prices for these earlier deals, particularly in oncology, have been driven up by the fierce competition for these assets, with the largest upfront payment, $640 million for a global collaboration to develop and commercialize an immuno-oncology asset in Phase 1 and potentially others in preclinical development, paid by Sanofi to Regeneron (see more detail below). (Source: FirstWord Pharma)

4. Alliances provide a significant source of funding and risk mitigation for emerging biotech companies – and for large pharma, who sometimes engage in strategic re-focusing of their pipelines and out-license numerous assets, as AstraZeneca did with 10 out-licensing deals in 2015. (Source: FirstWord Pharma)

5. Some notable recent deals are described in section B below.

B. Recent deal examples

1. Regeneron and Sanofi – global collaboration on Regeneron's early stage immuno-oncology assets

i. The parties share development costs (50% R Regeneron, 50% Sanofi) for Regeneron's Phase I PD-1 inhibitor, and Sanofi will also pay sales milestones subject to a $2 billion threshold.

ii. They also share discovery and early development costs (25% Regeneron, 75% Sanofi) to bring new antibodies and antibody combinations to proof of concept, and Sanofi may opt-in assets for further development funding.

iii. As new assets are opted in, the parties will alternate being the lead on US commercialization. Where Regeneron leads, it will book US sales and the parties will equally share the remaining development costs.

iv. Where Sanofi leads, it will book all sales and will fund 100% of the further development costs, with Regeneron repaying 50% of such cost from its share of the collaboration profits, capped at payments equaling 10% of Regeneron's share per year.

    1. The parties share the profits from sales of these assets equally.

    2. Regeneron retains a co-promotion right for US and ex-US markets.

v. Regeneron and Sanofi are also continuing their 2009 collaboration in this space, while reallocating some of that deal's funding toward the new deal's assets.

2. Juno and Celgene – global collaboration on immunotherapies for cancer and autoimmune disease

    i. Celgene pays upfront consideration valued at $1 billion, combining $150 million in cash and an equity investment, which includes a seat on Juno's board and which may increase over time up to 30% ownership stake in Juno.

    ii. Celgene gains an option to commercialize selected Juno assets outside North America, paying Juno a royalty as well as covering development and commercialization costs for that region, and to co-promote up to 3 programs globally, in an equal share of profits and costs.

    iii. Juno gains an option to co-develop and co-promote selected Celgene assets, sharing profits and costs (70%

Celgene, 30% Juno). Juno's co-promotion right is limited to the US and certain EU countries.

3. Hanmi/Sanofi, Hanmi/Janssen and Hanmi/Eli Lilly – licensing collaborations for a portfolio of Hanmi long-acting diabetes assets (Sanofi), a biological asset in diabetes (Janssen), and a small molecule for autoimmune diseases (Lilly)
    i. More "traditional" license and development agreement structures from a major Korean biotech.
    ii. Sanofi makes an upfront payment of 400 million Euros and commits to a series of development, regulatory and sales milestones up to 3.5 billion Euro, plus double digit royalties. Hanmi retains an exclusive right to co-commercialize the assets in Korea and China.
    iii. Janssen pays $105 million up front, and other milestones up to $815 million plus royalties. Hanmi retains rights in Korea and China.
    iv. Lilly pays $50 million up front, and other milestones up to $640 million, plus double digit royalties. Hanmi retains rights in Korea, China, Taiwan and Hong Kong.
4. Blueprint Medicines/Roche – collaboration and license agreement for cancer immunotherapy
    i. In March 2016, Blueprint Medicines and Roche entered into a collaboration and license agreement, under which Roche was granted up to 5 option rights to obtain an exclusive license to exploit products in the field of cancer immunotherapy.
    ii. Blueprint Medicines received an upfront payment of $45.0 million and is eligible to receive up to approximately $965.0 million in contingent option fees and milestone payments, plus tiered royalties on future net sales of products.
    iii. For up to 3 of the 5 collaboration programs, if Roche exercises its option, Roche receives worldwide, exclusive commercialization rights.
    iv. For up to 2 of the 5 collaboration programs, if Roche exercises its option, Blueprint Medicines retains

commercialization rights in the U.S., and Roche receives commercialization rights outside of the U.S.

v. Prior to Roche's exercise of an option, Blueprint Medicines has lead responsibility for drug discovery and preclinical development of all collaboration programs.

vi. Blueprint Medicines has lead responsibility for the conduct of all Phase 1 clinical trials other than those Phase 1 clinical trials for any combination products with Roche's portfolio of therapeutics, for which Roche has the right to lead such trials. Parties share the costs of Phase 1 development for each collaboration program.

vii. Roche is responsible for post-Phase 1 development costs for each product for which it retains global commercialization rights. Blueprint Medicines and Roche share post-Phase 1 development costs for each product for which the Company retains U.S. commercialization rights.

C. Research/Development Plan

1. Objectives

i. Clarify for both parties what they are trying to accomplish together

ii. Clearly set forth the rules that will govern the collaborative effect

1. Set forth the scientific objectives

2. Describe the approaches that will be undertaken and the methodologies that will be used

3. Quantify the work to be done (e.g. number of replications, number of subjects, etc.)

4. Specify who is responsible for what activities – also identify decision makers

5. Specify the due dates for completing each part of the research project – assists in managing resource allocation and prevents lost time

6. Specify go/no go decisions

7. Provide benchmarks – measures work progress

8. Include alternatives to address experimental failures/ obstacles

2. Status
   i. Draft version in the signed deal – motivation was to get the deal done
   ii. Failure to update
      1. Recommend having a date and person assigned to update the research plan in the contract.
      2. Alternative is making Joint Development Committee responsible for updating on a defined basis and getting approval by Joint Steering Committee
3. Issues
   i. Who is the drafter?
      1. Business Development
      2. Lawyers
      3. Scientists/Clinical Team
         a. Jointly between the collaborating researchers
         b. Preferred drafters
            i. They are the ones who really understand the complexity of what is to be undertaken
            ii. They must fully embrace the plan that is being developed
   ii. IP is generally tied to the research plan unless deal is focused on a clinical compound
   iii. Need to define know-how
   iv. Need to define how to deal with blocking IP
   v. Need to ensure that the described research plan covers the IP generated, otherwise there may be ownership issues
   vi. Need to be certain that no blocking IP is inadvertently brought into the research plan by the collaborator

vii. Need to balance the benefits of a well described research plan against the benefits of providing sufficient flexibility to advance the program efficiently as circumstances change

viii. No ownership and/or buy-in of the research plan

1. Scientist, if not a drafter, may not understand the business aspects of the deal and does not believe the drafter understands what is entailed in doing the science

2. No roles or responsibilities are defined, therefore no accountability

a. Parties may have unrealistic expectations and become frustrated.

b. If unclear as to responsibility, each party may sit back and wait in vain for the other party to produce

3. Consequence is failure to meet the goals of the parties and the deal fails

a. Studies show that greater than 50% of all partnerships/alliances fail

i. Poor planning

ii. Slow speed at which results materialized

iii. Changes in management team

ix. Metrics Driver

1. Financials and milestones are generally tied to the research plan so it is critical that the attorney understand the goals of the research plan

2. Type of deal

a. Solely risk sharing, e.g., milestone driven, money is the leading factor not the science (short cutting on experiments not well defined in the research plan)

b. Sharing of development/operations costs – money is less of issue but it is still important to define "costs" that are shared

x. Accountability – for the relationship/deal overall

1. Recommendation – have a single person oversight of deal from start to finish, preferably a key stake holder. Ensure clear communication of the nature of the business deal to broader implementing team, including around publication, when consents are needed, scope of the license, non-competes, etc.

2. For licensees, determine whether any firewalls are needed between the licensed program and any on-going internal programs in order avoid taint

4. Novel Technologies

i. Research plan is "indefinable" as the deliverables cannot be quantified; there are no conventional or clear milestones, e.g., clinical results or any comparables.

1. Parties are used to having measurably known quantities to have a comfort level that the project is advancing – may impact the collaboration relationship.

2. Go/No go criteria not defined – alternatives or next steps are not thought through – without this significant time and money resources can be wasted.

3. As milestones cannot be effectively set, the milestones tend to constantly be shifting based on new data making it difficult to reach the milestone.

ii. Tension as IP attorneys want to protect any IP before it is disclosed (in a deal), yet patents may not be sufficient to protect (e.g., know-how) – raises confidentiality and privilege issues

iii. Difficult to get reps and warranties

iv. No experts to provide guidance

5. IP Ownership Issues

i. Joint ownership

1. Prevent blocking IP

2. Challenges

a. Each party can practice or use the IP or separately sell, license or transfer the IP (even to a competitor) without consent from or a duty of accounting to the other party

b. All parties must sue an infringer

c. Warranties require full ownership

d. Rules vary from country to country

3. Alternatives

a. One party owns and licenses to the other – needs to be co-exclusive license and need to consider right to grant sublicenses.

b. Divide up the IP and cross-license each other, critical IP may go to the other party and/or they can license to another

i. If the party owning the IP does not want to continue prosecution of a particular patent and/or IP in a particular territory consider impact of having the rights transfer to the other party.

ii. If the licensee creates critical IP that would extend patent life cycle consider implications in a reversion of rights.

c. Consider a special purpose vehicle or special purpose entity to jointly own the IP

d. Consider standstill provisions that preclude the parties from prosecuting/enforcing patents or practicing, licensing or transferring the IP outside of the relationship

iii. Country-specific IP rules

1. You need to know who owns the IP, the individual or the company – each country has different rules

2. Assignment language is country-specific

a. A present assignment of a future right is not valid is some countries

3. Different countries have different disclosure rights and obligations may depend on the disclosure rights
4. Compensation requirements for inventions may vary from country to country
5. Legality of waivers of IP rights vary

iv. IP ownership which varies from contract to contract, with the same party covering overlapping scope of work

6. Change of Control Issues

i. Change in players – makes communication and continuity difficult

1. need proper leadership – to show ongoing commitment with a focus on a collaborative climate and removal of barriers
2. performance management – owning outcomes and recognizing and reinforcing desired behaviors

ii. Change in strategy

1. Over committed
2. Inconsistent with business objectives
3. Rework or terminate the deal

iii. Competitive programs or products

iv. Pharma's change of control increasingly an issue to consider

v. Consider IP leakage to or from an Acquirer

vi. Consider application of exclusivity or noncompetition provisions to an Acquirer

D. Governance

1. Needed to manage the relationship between the parties and to ensure a clear decision making process
2. Joint Steering Committee ("JSC")

i. Typically set number of members from each party

1. should be selected by the stake holder
2. roles and responsibilities should be defined

3. should understand the science, the company business, and have the time to participate
    a. principal investigator or chief scientist, preferably someone who has already invested into the program so has buy-in
    b. a senior business or executive of the company empowered to make decisions regarding the collaboration

ii. Tie breaker vote – generally governed by ownership and control rights
1. One party to the deal
    a. Chair
    b. Funding party
    c. Senior executives in the company
2. Independent expert
3. Can be allocated to different parties depending on the significance of the issue
    a. Termination of the collaboration
    b. Change in research direction – significantly impacting resources
    c. Safety decision-making

iii. Sub-committees
1. Joint Research Committee ("JRC")
2. Joint Development Committee ("JDC")
3. Joint Clinical Committee ("JCC")
4. Joint Commercialization Committee
5. Can also have separate subcommittees for specialty topics such as IP, Regulatory and Finance
6. Joint Project Team; Working Groups

3. Governing Strategy

i. Top down – JSC determines the research work and tells the "team" what they are going to do – the challenge with this strategy tends to be in the failure to explain to the

"team" why they are doing what they are doing – less buy-in

ii. Bottom up – team provides recommendations for moving forward, more buy-in to the project, JSC agrees or disagree

4. Duties of the JSC
   i. Agreeing on research plan
   ii. Reviewing goals and strategies of collaboration
   iii. Facilitating technology and/or information transfer
   iv. Receiving deliverables under the research plan
   v. Reviewing publications
   vi. Reviewing and allocating financial and personnel resources
   vii. Resolving disputes
   viii. Determining whether milestones have been met and/or finalizing milestones
   ix. Deciding on size, number, or type of clinical trials
   x. Dealing with field of use limitations (territorial, indications) – if one has split territories or indications may impact the other party
   xi. Deciding on early termination e.g., due to research failure, safety/efficacy concerns, change in business directions, etc.
5. Agreement should include:
   i. Composition of the Committee
   ii. Meetings
      1. Set number and times preferable
      2. Allocation of cost
   iii. Dispute resolution process - voting, veto, escalation, and tie breaking rights
   iv. Instructions regarding preparing/finalizing the work plan
   v. Definition of areas of joint control and divided responsibilities e.g., allocate regulatory and compliance issues

6. Governance factors that typically contribute to failure of the relationship
    i. JSC or subcommittee membership changes
    ii. Lack of accountability

E. Due Diligence
1. Why have diligence obligations?
    i. Diligence obligations are important to a licensor granting an exclusive license that is not fully paid because, in the absence of diligence, the licensee might shelve the product and the licensor would never receive those additional payments that are dependent upon developing or selling the product
    ii. Substantial license maintenance payments can be a substitute for diligence but life sciences licensees are frequently hesitant to agree to large license maintenance payments due to the uncertainty re when the product will be approved, the scope of the label and pricing/ reimbursement issues
    iii. Diligence obligations are rare in simple non-exclusive licenses because the licensor can always extract additional value from the IP by granting additional licenses.
2. What kind of diligence obligations?
    i. Obligation to diligently sell: but can't sell until get regulatory approval
    ii. Obligation to seek or obtain regulatory approval: but can't get approval until you have data meriting approval and, even when the data is available and the filing is made, it is not clear how long it will take to get approval from the FDA
    iii. Obligation to perform testing to obtain data sufficient to obtain regulatory approval: but things don't always work as planned
    iv. Obligation to achieve anything else that results in a payment to licensor
    v. Licensor can also have diligence obligations such as performance of research obligations, or smooth and timely

transfer of technology, know-how, regulatory registrations/ licenses, data, etc.

3. Commercially reasonable efforts
    i. The most common solution to the problem
    ii. Efforts that would be devoted to a similar product at a similar stage in its development with a similar market potential
    iii. Relative to efforts of companies in the industry or the licensee?
    iv. What other factors should be considered?
    v. Breach is hard to prove
4. Objective diligence criteria
    i. An absolute obligation to achieve a particular goal by a particular time
    ii. Breach is clear
    iii. If effect of breach is termination of the license, then licensee will only agree if achievement is within its control
    iv. Control points include:
        1. initiating clinical trial
        2. filing for regulatory approval within certain time after completing pivotal clinical trial
        3. filing for pricing approval within certain time after completing reimbursement study
        4. launching within certain time after receiving approval
        5. employing a number of sales representatives
5. Compromise positions
    i. Providing mechanisms for getting extension of time
    ii. Providing a buffer between breach and termination
    iii. Making obligation to use good faith diligent efforts to achieve a particular goal by a particular time
    iv. Making money a surrogate for diligence
        1. Minimum spend on program is evidence of diligence

a. Appropriate spending varies according to stage of development/commercialization

b. Minimum payments to licensor to avoid termination, creditable against next milestone

v. Self-help vs. termination: licensor's right to develop and/or commercialize in certain indications

II. TRANSITIONING PHARMACEUTICAL PRODUCTS/PROGRAMS

A. Context

1. Transitions are necessary because this isn't just a license to a patent; it's a license to all rights to a pharmaceutical product/program and such rights may include know-how, biological materials, regulatory approvals, contracts, manufacturing rights/access and more

2. Degree of complexity varies with the maturity of the product/program

3. Transition from licensor to licensee:

i. Will happen right after license agreement is signed, if licensee will do all work post-signing

ii. Will happen later if the agreement contemplates a period in which the licensor conducts research or development and the licensee takes over after the end of such period

4. Transition from licensee to licensor happens after the agreement terminates or there is a reversion event (e.g., one product or a portion of the territory reverts to the licensor)

5. Transitions can be complicated

B. Scope of returns and retained rights

1. Patents

i. Transition to licensee

1. Licensor usually grants a license to licensee, so no assignment of patents

2. Licensee may take over patent prosecution or maintenance

a. Transfer of patent files

b. May need to coordinate if licensee's rights are limited to a particular territory

c. May need to coordinate if patents cover platform technology that may be used by the licensor or other partners/licensees

2. Transition to licensor

i. License to licensee is terminated

ii. Licensee to grant license to licensor under licensee's patents needed to continue development, manufacture or commercialization of product or licensee may assign its rights to IP it generated covering the product.

1. May need to ensure that IP is prosecuted in countries desired by the party (i.e., licensor) continuing with the product.

iii. License grant may occur automatically upon termination or at licensor's election following termination. Consider timing and circumstance of this election.

iv. License may be royalty-bearing: negotiate royalty rate now or later?

3. Know-How

i. Transition to licensee

1. Licensor usually grants a license to licensee but license isn't useful if licensee doesn't have/know the know-how

2. Provide copies of data, protocols, etc.

3. May need a technology transfer to teach how work is performed

4. Ongoing disclosure obligations if licensor continues to do work

ii. Transition to licensor

1. License to licensee is terminated

2. Data, protocols, etc. provided by licensor are returned or destroyed

3. Licensee to grant license to licensor under licensee's know-how needed to continue development, manufacture or commercialization of product, but license isn't useful if licensor doesn't have/know the know-how
4. License may be royalty-bearing: negotiate royalty rate now or later?
5. Provide copies of licensee's data, case report forms, protocols, etc.
6. May need a technology transfer to teach how work is performed

4. Biological materials
   i. Same issues as know-how but consider:
      1. Is there a finite amount available?
      2. Are they self-replicating?
      3. Creation of derivatives
5. INDs, NDAs and other regulatory approvals
   i. Need to follow official procedures for transferring
   ii. Timing of transfer
6. Contracts
   i. Contracts with service providers to perform experiments, collect, analyze or store data, collect and store samples, etc.
   ii. Simplest to assign/novate contract to party that is getting the product rights
   iii. Issue if contract covers multiple products (e.g. master service agreement)
   iv. Issue if not assignable
   v. Consider translation issues if contracts not in English (e.g., clinical trial agreement internationally) and conflict issues if there are confidentiality provisions or non-compete provisions that impact assignment or assumption.
7. Supply of Product
   i. Sell inventory at cost

ii. Many technical and regulatory issues to obtaining product from another source (see below for more detail)

iii. May need to provide interim supply

8. Safety Data Exchange

i. Consider retaining the transferring party to do data management activities, e.g., coding, creation of CFRs, data validation, transfer, reporting etc. until database lock.

ii. Address who will maintain the archive data for purposes of response regarding regulatory matters.

iii. Critical to set up timelines and coordination of activities.

C. Clinical stage products

1. Stages

Preclinical – testing of experimental drugs usually in animals to determine safety and dosing prior to use in humans.

Phase I - safety

Phase II - safety, dosing, effectiveness and adverse events

Phase III - therapeutic profile of drug, including contraindications, warnings and limitations on use.

Phase IV – post-marketing studies to delineate additional information including the drug's risk, and optimal use. (21 CFR §312.85)

2. Agencies/Parties Involved

i. FDA

1. Filings

a. IND - Investigational New Drug Application (IND) using FDA Form 1571 (available at *www.fda.gov/cder/regulatory/applications/Forms.htm*), which includes

i. Animal Pharmacology & Toxicology studies – preclinical data to assess safety in humans

ii. Manufacturing information – composition, manufacturer, stability , controls

iii. Clinical protocols and Investigator information - to assess risks, qualifications of investigators and commitments to obtain consent from patients, and to obtain oversight by an institutional review board (IRB)

b. ANDA - An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product.

c. NDA - The New Drug Application (NDA) is the vehicle in the United States through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing

2. Statutory Powers

a. Seize any drug that is adulterated or misbranded (*21 USC § 334*).

b. Enter any factory, warehouse or establishment in which drugs are manufactured, processed, packed or any vehicle used to transport or hold such products *(21 USC § 374(a)(1)*).

c. Inspect at reasonable times facility or vehicle (above) and all equipment and materials (*21 USC § 374(a)(1)*).

d. Collect samples of drug products (*21 USC§ 372(b)*).

e. Inspect records, files, papers, processes, controls and facilities related to drug products (*21 USC § 374(a)(1)*).

f. Inspect records, files, papers, processes, controls and facilities related to drug products (*21 USC § 374(a)(1)*).

3. Sponsor

4. Investigator

5. CRO(s)
6. Patient
7. Manufacturer
    i. Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 351 (a)(2)(B)) requires drugs, which include IND products, to comply with current good manufacturing practice as follows:

    A drug...shall be deemed adulterated...if...the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

    ii. The CGMP regulations for drug and biological products are in 21 CFR parts 210 and 211 (applies to Phase II, Phase III and commercial products)

    iii. (CGMP) requirements of the Act (21 U.S.C. 351(a)(2)(B)) and CFR states that:

        1. manufacturers must comply with relevant CGMP validation and recordkeeping requirements and

        2. ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection;

    iv. Under CGMP, if a sponsor or manufacturer initiates a contract with another party to perform part or all of the phase 1 investigational drug manufacturing, the sponsor or manufacturer, and contractor are both responsible for assuring that the phase 1 investigational drug is manufactured in compliance with CGMP.

    v. Types of Manufacturers – for a single product

        1. API – Active Pharmaceutical Ingredient, Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or

to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient

2. Process or Formulation activities (e.g., place the identifying information on the dosage form itself

3. Packaging (e.g. drug product containers, closures, packaging materials, package drug products)

4. Sites that test components, e.g., those performing physical, chemical, biological, and microbiological testing to monitor, accept, or reject materials, as well as those performing stability testing

vi. FDA recommends that a move to a different manufacturing site, when it is a type of site routinely subject to FDA inspection, be submitted as a prior approval supplement if

1. the new manufacturing site has never been inspected by FDA for the type of operation being moved,

2. the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years, or

3. the new manufacturing site does not have a satisfactory current good manufacturing practice (CGMP) inspection for the type of operation being moved.

vii. Changes to an NDA or ANDA - (21 CFR 314.70) to conform to section 506A of the FDA Modernization Act of 1997 provides the requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes.

1. CDER must be notified when a manufacturer changes to a manufacturing site that is different from those specified in the approved application (314.70(a))

viii. If changing manufacturing site – need to factor in the time for new site to become CGMP certified

8. Liabilities
    i. Civil Issues
        1. Contractual
            a. Contract with the patient - Consent Form
            b. Contract between the party assuming the IND and the assumed liability and adequate insurance.
            c. Must maintain same GMP manufacturer and/ or notify FDA and amend IND
        2. Parties can contract regarding the liability but one party is still responsible. FDA will look to the sponsor.
    ii. Ethical responsibilities
        1. Patient
            a. Abandonment - civil liability will depend on the language in the consent form.
            b. Consider a compassionate use IND.
            c. Closing a trial does not require FDA approval but does require notification.
            d. Stop enrollment
            e. Transfer of sponsorship.
        2. Other Liability Issues
            a. IND Filing - 1571 Form - "I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in

accordance with all other applicable regulatory requirements."

b. Investigator Form (FDA Form 1572) (*21 CFR § 312.53(c)*). The investigator must agree to conduct the study in accordance with the protocol, report any adverse experiences, and maintain adequate and accurate records. In addition, informed consent must be obtained from each study subject who will be administered the investigational drug (*21 CFR § 312.60*). An Institutional Review Board (IRB) must also review and approve all clinical studies before an investigator begins conducting

iii. Consequences of FDA Breach

1. Issue a warning letter threatening court action if corrections are not made
2. May result in investors becoming skittish
3. Initiate regulatory actions. – e.g., a warning letter to the sponsor or 3rd parties (investigators) who participated.
4. Seizure of the product and enjoining manufacture
5. Impose fines after an administrative hearing (*21 CFR § 17.1*).
6. Suspend, revoke or fail to approve an application to market a drug.
7. A violation that occurs during a study can raise questions regarding its validity, even if errors were made by independent clinical investigators.
8. Failure to timely report serious adverse events can result in increased reporting obligations.
9. Criminal prosecution – any violation of the FDC Action is a criminal violation. (e.g., there has been patient injury, the company has a history of repeated violations, or the company has falsified records or lied to the FDA.

10. Furthermore, under a unique feature of the FDC Act, FDA can punish an individual who did not personally commit a violation, but who was in a "responsible position." Thus, FDA can bring actions against company presidents based primarily on their title, rather than direct culpability

9. Things to consider when drafting the "transfer" agreement (preferably in the initial deal agreement). THINK ABOUT THE DIVORCE AT THE WEDDING

   i. Generally, the lawyers and deal team think about what can go wrong, e.g., bankruptcy or if one does not hit a milestone, and one party exercises its contractual right to walk away (i.e., they plan for a termination but the details many times are not worked out). Consider outlining what the obligations are upon reversion in the initial deal contract.

   ii. Typically, reversion rights vary from contract to contract and depends on the reason for termination of the relationship

      1. Diligence obligation – Company will use the same diligences as they would for their own compound (provides leeway not to proceed usually comes with some monetary penalties)

      2. Safety reasons (generally no reversion rights)

      3. Commercial viability factors e.g., regulatory hurdles so great - an outcome study is required the cost of which exceed the value of the compound or another competitor put a competing product on the market first

      4. A product is placed on hold when e.g., waiting for an event in the market place.

      5. Manufacturing is shut down (e.g., non-compliance with CGMP) then impossibility of performance.

   iii. Factors to consider

      1. Providing for a termination steering committee within X days of notification of termination to

shepherd down the wind down and responsibilities (in essence plan for the divorce)

2. Who, What & When
    a. Who - the contact person (facilitator) for each party
    b. What - scope of materials to be transferred
    c. When - length of time
3. Putting together a checklist
    a. What is the appropriate termination/transition period upon notice?
    b. If the compound is in clinical stage and/or are there are marketing authorization in the US and worldwide – the "transition committee" needs to think about the mechanism of notifying and working with the various regulatory authorities.
        i. Risk – if you agree to use good faith efforts without setting forth a time period it can be for a significant period of time.
        ii. Consider putting in a time limit for the "use of good faith efforts" in the event that these efforts fail
        iii. If on-going clinical trial(s), will the clinical trial(s) continue to be run or financially supported by one of the parties?
            1. What is the mechanism of transfer?
            2. Does the transferor have the right to discontinue the trial and/or cease enrollment?
            3. Who are the stake holders that need to be informed and advised?
                a. Partner
                b. Regulatory agencies

c. Contractors –CROs, manufacturer(s), test sites, etc.

d. IRB – Institutional Review Board

e. Clinical Sites

f. Principle investigator(s)

g. Public Affairs (if material then a press release is necessary)

h. Clinicaltrials.gov (industry wide FDA mandate that all clinical studies be publicly disclosed) (outcomes sought, duration, sites, etc.)

4. What about data bases, documents, and regulatory correspondence

   a. Are there any customer, hospital or government contracts that can be assigned? If not, what do you do with those?

5. If you are in the midst of an agreement and the other party is unwilling to assign, then you may still be obligated to pay the cost.

   a. If you are in clinical trials but about to launch the product, what about the sales training materials

      i. As the purchaser/transferee, you want to have those materials, as well as information on projected pricing, list of opinion leaders in the market

      ii. Clinical protocol

4. What if the compound has safety issues and there are reversion rights?

5. Are there non-compete clauses in the initial agreement?

iv. Deliverables if a transfer is necessitated - what if any is the language negotiated in the contract between the parties?

v. Negotiations

1. Transferring Entity

a. Preference - we give back what you gave us (e.g., the product) if it is a reversion of a licensed in product and that is all

b. Reason – transfer takes significant resources

c. Transferring entity has contractual obligations still to FDA and must satisfy those requirements, but no obligation to give any data (e.g., raw data from clinical trial) or materials with the licensed product if not contracted at the onset

d. If contract language only states that the compound reverts – there is no duty to transfer any information.

e. Negotiate to minimize liability if transferring data (or even if just transferring rights back to the compound).

i. To the extent data is transferred provide no reps or warranties – caveat emptor

ii. Request indemnification – you do not know how the Acquirer is going to use the data and you do not want to be liable if they are sued.

f. If terminating a licensed-in product, considering negotiating only a termination fee for failure to proceed with the product as opposed to any transfer obligations.

g. If the transferring entity is also the manufacturer – may negotiate to retain rights to manufacture and to royalties

h. If selling an asset consider doing and audit to identify and address any issues, so if necessary can warrant that there are no unexpected issue with quality of data.

2. Licensor or Acquirer

a. Prefer all the information and data on the compound.

b. If expecting a lot negotiate it upfront when setting up the initial deal

i. Representative contract language: "Upon termination Licensee shall give the right and license to Licensor under any Licensee patents, applications and know-how at the time of termination and to independent Licensee IP useful for the development, manufacture, use, or sale of Product, and Licensee agrees to reasonably cooperate in order for Licensor to develop and manufacture Product, and such cooperation shall include without limitation, transferring INDs and all data, licensing of all trademarks, trade dress and packing materials, provide clinical samples and assist in regulatory compliance. . ."

ii. If acquiring, do an audit of the study – know what you are buying.

3. Buyer Beware

a. You may be liable if there are FCPA and Anti-kickback, Sunshine Act or FDA Bioresearch Monitoring (BIMO) inspection violations

b. Criminal fraud convictions are on the rise and acquittal rates are on average less than 2%

c. Recovery based on total fines are on the order of billions per year

D. Commercial stage products

1. Overview

i. What's different about marketed pharmaceutical products?

1. The patients:

a. Any interruption in their access to the drug could be devastating to them personally

b. If they need to take another drug while yours is unavailable, they may not have any incentive to return to yours

2. The prescribers:

a. Make prescribing decisions based upon several factors including reliability and reimbursement status

ii. Many common transfer issues with clinical stage products, but the magnitude of these issues is often significantly larger

iii. Several additional transfer issues

iv. The size of the task depends upon the number of countries in which the product is sold and the number of patients who are taking the drug

v. Categories of things to be transferred

1. Manufacture and supply chain

2. Distribution chain

3. Regulatory approvals & fulfillment of regulatory obligations

4. Commercial infrastructure: Sales force, promotional activities, sales records, financial accounting

5. Medicare/Medicaid coverage, insurance company reimbursement

6. Patient support functions

vi. Bottom line: Transferring a commercialized pharmaceutical product is a logistically challenging task that

requires careful planning and a transition period of several months

2. Manufacture and supply chain
    i. All manufacturing issues for clinical supply apply here
    ii. Existing packaged materials have name of former seller
    iii. Need regulatory approval to change label, so will need to sell under existing label until approval received
    iv. Will former seller continue to sell until newly labeled product is available?
3. Distribution chain
    i. Need to assign existing distribution agreements or enter into new ones (with existing or new distributors)
    ii. Need to address inventory held by existing distributors
    iii. Need to get new inventory to new distributors
4. Regulatory approvals & fulfillment of regulatory obligations
    i. There's a separate regulatory approval in each country of sale
    ii. Need to follow each country's rules re transferring the regulatory approval
    iii. Once the approval is transferred, the new owner is responsible for all reporting to the regulatory agency, including adverse events, but will new owner have the infrastructure to fulfill such obligations?
        1. Consider having old owner continue duties until new owner has the safety database and an adverse event tracking and reporting system in place
5. Commercial infrastructure:
    i. Sales force
        1. Need to hire away existing sales representatives or to hire and train new ones
        2. Training should be consistent with past practices, so need to have training materials transferred to new selling party

3. Also need records re past sales calls and prescriber preferences/track record

ii. Promotional activities

1. Marketing reports, reimbursement studies and promotional materials should be transferred, along with rights to use, reproduce and modify

2. Ongoing and planned advertising campaigns should be completed, transferred or terminated

iii. Product trademarks and web domain names

1. Need to be licensed or assigned to new selling party

2. Trademark files need to be transferred

3. Does old selling party retain goodwill or other interest in the trademark (including a royalty stream)?

4. Old selling party should be prohibited from using similar trademarks or domain names

iv. Sales records

1. Need to be transferred to new selling party

2. In case of a recall or other issue, need to keep track of which patients received which products (note that handling of and liability for recalls should also be separately negotiated)

v. Financial accounting

1. Need to transfer full financial database

2. Need to establish procedures for handling returns

3. Need to address post-termination sales made by old selling party and returns accepted by new selling party for product sold by old selling party

6. Medicare/Medicaid coverage, insurance company reimbursement

i. Need to assign or enter into new agreements with government and private insurers re coverage and reimbursement amount/conditions

7. Patient support functions
    i. Need patients to have continuity of access to medical professionals who can answer questions and provide advice
    ii. Consider assigning or arranging automatic forwarding for toll-free phone numbers, live chat or email inquiry addresses
    iii. Engage experts and knowledge leaders involved in product positioning/visibility prior to transfer

NOTES