



Biotechnology Alliances:

Co-Development And Co-Marketing Agreements

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1. INTRODUCTION

In transactions between technology companies and large pharmaceutical companies, it is very common to mix the following elements:

- Licensing of intellectual property rights
- Joint research and development
- Joint promotion and marketing
- Shared manufacturing and product supply.

In straight licensing agreements, compensation is typically by way of up-front fees, milestone payments and royalties. In more sophisticated agreements that involve joint research and development and commercialization activities, it is much more common for the compensation to include payment for research and development costs, contribution of resources and technology and investments by way of loans, convertible debt or equity. Previous papers in this conference have dealt with equity financing and with straight licensing so these topics will not be canvassed in great detail here.¹

(a) Why Enter Into Co-Development and Co-Marketing Agreements?

It is critical for any lawyer assisting biotechnology companies with transactions to have a detailed and comprehensive understanding of joint development and commercialization agreements for a number of reasons:

- There is often very little value created for a biotech company merely by performing a straight licence of an unvalidated genomic target (i.e. where there are no therapeutic products (drugs) associated with the target). Typical valuations would indicate that the value of a target is usually in the range of US\$250,000 to US\$2,000,000. The economic reason that so little value is placed on early stage technology is quite clear. First, experience in the last 10 years has show that unvalidated genetic targets rarely lead to effective clinical products (clinical products could include therapeutics, diagnostics and other products such as palliative medicines).² Biological systems have turned out to be much more complicated than was thought a generation ago. Diseases often entail a number of gene or gene components working in combination. Whether these genetic

¹ This paper will primarily address issues arising in biotechnology co-development and co-marketing agreements. To some extent, many of these issues are also relevant in the context of evaluation agreements, contract research agreements, material transfer agreements, however, space and time limitations do not permit an extensive treatment of these other types of agreements.

² This paper focuses on diagnostics and therapeutics for human populations, however, many of the concepts used will also be applicable in veterinary and agricultural biotechnology.

targets give rise to proteins and biological pathways that are “drugable” is often very hard to predict. It is also very hard to predict the potency, safety, solubility, absorption and metabolic stability of biotechnology derived therapeutics.

- Some common estimates of the cost of generating a new drug place that cost at around \$US450,000,000 (other estimates range as high as US\$800 million). The table below gives a rough approximation of how those costs are typically incurred.

Cost of New Drug Development

Activity	Typical Cumulative Cost (US Dollars)
Lead Generation (<i>Note 1</i>)	\$50 million
Lead Optimization	\$150 million
Animal Studies	\$165 million
Pre-clinical (<i>Note 2</i>)	\$205 million
Phase 1	\$230 million
Phase 2	\$260 million
Phase 3 (and development of manufacturing process)	\$390 million
NDA/Launch	\$450 million

Note 1 - Includes target identification

Note 2 - Includes thorough in-vitro ADMET (absorption, metabolization and toxicity) screening, preliminary manufacturing and drug delivery planning.

- It can be noted that over half of the costs are incurred prior to the completion of Phase 2. However, failure rates in Phase 2 and Phase 3 are very high. As such, licensees of early stage compounds³, especially those that have not registered an IND, usually argue with substantial reasonableness, that given the risks and costs yet to be incurred, it is uneconomic to offer favourable licensing terms.

³ Throughout the paper I use the word “compound”, however, this should be understood to include small molecules, protein products, anti-bodies and any other biological active substance.

- The majority of risks and costs in the process occur in lead optimization, animal studies, pre-clinical work and regulatory approval. Young biotech companies have often licensed out their technology prior to these stages and given away most of their intellectual property rights. These deals do not create a large amount of value for the biotechnology companies. (Although in certain circumstances it is necessary for the biotech company to enter into this type of agreement) In order to capture a reasonable proportion of the upside arising from commercialized biotechnology products, a biotech company has to participate in, and bear a portion of the costs and risks related to, development activities such as lead generation, authorization, animal studies and pre-clinical work.
- It is very difficult to build sustainable, competitive advantage in an early stage biotechnology company. Current estimates suggest that there are about 2,000 small biotech companies in North America. Often these companies start out with some intellectual property around some specific genetic targets or with a very narrow, but unique, set of enabling technologies. Unless the early stage company develops capacity and expertise in target validation, lead generation, lead optimization, development and commercialization, it is unlikely that they will ever generate extensive returns for their founders and shareholders. Small biotech companies need to participate in joint development and commercialization activities in order to get the experience and expertise that are required so that their companies can continue to evolve towards more successful and sustainable business models.
- Finally, advances in genomics technology and bioinformatics such as high throughput screening methods have created a flood of biotechnology related information and data. The challenge for all parties involved in the innovation process is to turn this flood of data into profitable commercial products. Smaller biotechnology companies are realizing that they need to gain expertise in development and commercialization in order to better understand how they can generate effective information and use it to create commercial opportunities.

(b) Difficulties in Crafting Effective Agreements

As described above, there are a number of clear incentives for biotechnology companies to enter into joint development and commercialization agreements with larger pharmaceutical companies. At the same time, a number of factors and issues make it difficult to craft effective agreements in this area:

- There are often great uncertainties about the technology will evolve and how research programs should be conducted.
- The parties may have some substantial differences in the strategic intent behind joint development and commercialization agreements. For example, large pharmaceutical companies often want to gain access to a greater portion of intellectual property rights belonging to the biotech company than is reasonable given the biotech company's concern for its future (e.g. they may seek all platforms and all products). At the same time, large pharmaceutical companies may be hesitant if the project is seen merely as an opportunity for it to teach later stage development and marketing to a small biotech company.

- Many alliances between partners of disproportionate sizes struggle to bridge the perceived gap of the larger partner's bureaucracy and the smaller partner's unconventional operational methods. Frequently, the smaller party, because of constrained resources, has been forced to cut a few corners. This creates concerns on behalf of the larger partner about its ability to successfully obtain regulatory approval and to assess risk. At the same time, the smaller party has very legitimate concerns about being caught up in the cost and delays of satisfying the larger partner's bureaucratic requirements.
- Finally, the pharmaceutical industry tends to rely heavily on the creation of blockbuster products, i.e. products where worldwide sales exceed US\$500,000,000 per year. Rights to single products can have an enormous impact on the economic success of the parties. As well, any delays in the path to commercialization can have a tremendous impact.

Despite these obstacles, joint development and commercialization agreements continue to get done:

(c) Example: Vertex-Novartis

Vertex and Novartis entered into a series of agreements to discover, develop and commercialize small molecule drugs targeting protein kinases. The agreements included all therapeutic indications with some defined exceptions, mostly related to previous commitments made by Vertex. The agreements included a six year research term with an additional two years to complete early development. Vertex is responsible for drug discovery and clinical proof of concept testing of drug candidates. Novartis will get worldwide development, manufacturing and marketing rights to eight of these candidates and Vertex will get co-promotion rights in the U.S. and Europe. The agreement calls for a \$15,000,000 up-front payment and \$400,000,000 in research and development funding. Of the research and development funding, \$200,000,000 is for direct research support over six years and the balance is a \$200,000,000 loan facility for pre-clinical and early clinical development on compounds. The loan facility is interest free and is forgiven as more compounds are accepted for development by Novartis. Novartis will reimburse up to \$15,000,000 of Vertex's patent costs. Finally, the agreement calls for approximately \$400,000,000 in contingent license fee and milestone payments. As well, there is inflation adjustment on research support, license fees and milestones as well as substantial royalties on world-wide product sales.

The deal did not include any equity component, the Vertex drug discovery technology or any other components. Vertex was granted leadership of joint research committee and Novartis was granted leadership of the joint development and marketing committees. The agreement contained certain risk sharing provisions. If Novartis does not accept all eight compounds or eight compounds do not achieve proof of pharmacodynamic concept, certain portions of the loans are repayable to Novartis. On the other hand, if Vertex bears the cost of developing compounds to the end of Phase 2, i.e. Novartis has not exercised rights earlier in relation to the compounds and Novartis then wishes to exercise its rights, Vertex will receive increased manufacturing rights or joint venture rights on these later acquired compounds.

(d) Example: Bristol Myers Squibb and IMClone Systems

This transaction has received a tremendous amount of media attention. The transaction centered around IMClone's late stage drug ERBITUX which was directed towards colorectal, head and neck, pancreatic, lung and other cancers. It was a new form of drug, namely an epidermal growth factor inhibitor and was anticipated to have blockbuster potential. Recently, this drug suffered a regulatory set back when the US FDA requested that additional Phase 3 tests occur. Given the size of the deal, and some other aspects of the way compensation flowed into IMClone, these regulatory setbacks were treated in catastrophic terms by the media. The commercial agreement gave Bristol Myers Squibb rights to co-develop, co-promote and distribute ERBITUX in the US, Canada and Japan. Bristol Myers Squibb promised to pay up to one billion dollars in milestones, including \$200,000,000 upon execution of the agreement, \$300,000,000 upon acceptance of a BLA ("Biologics License Application") filing and \$500,000,000 on BLA marketing approval. As well, Bristol Myers Squibb shall pay 39% of annual net sales in USA and Canada to IMClone and Bristol Myers Squibb would be responsible for the costs of all registrational studies in the U.S. and Canada and for all sales, marketing and distribution costs. IMClone was given the right to supply the bulk product for commercial use, thereby improving its manufacturing capability. Bristol Myers Squibb and IMClone shared the development and marketing costs in Japan and the revenue from sales in equal portions. This transaction also had a very significant equity component. Bristol Myers Squibb acquired 14.4 million shares at US\$70.00 per share (a premium to the market price). Besides rights to govern co-development, co-promotion and distribution, Bristol Myers Squibb obtained rights to nominate directors to the IMClone board and to all board committees. Finally, Bristol Myers Squibb was granted a right of first offer on another significant IMClone product as well as a right of first negotiation on other products for five years.

After the regulatory problems arose, Bristol Myers Squibb attempted to renegotiate the deal. IMClone refused. It still remains to be seen what the ultimate resolution of this issue will be. However, this deal does illustrate a number of important concepts including the use of equity in these types of deals, the massive increase in deal size for late stage products with blockbuster potential, and the need to do thorough due diligence. It should be noted that although the popular press has portrayed this as a very one-sided deal in favour of IMClone, many industry participants think that the deal was balanced. The types of problems that ERBITUX has had in its Phase 3 testing are relatively common, especially for oncology treatments where combination treatments are quite common. (an issue in the ERBITUX Phase 3 trials was that because ERBITUX had been offered in combination with other traditional cancer treatments, the FDA required further clinical data to demonstrate the efficacy and benefits of ERBITUX.)

The rest of the paper does three things. First, we discuss some major ways that co-development and co-marketing agreements can be structured. Second, we discuss some significant terms that are often found in these types of agreements and provide some sample clauses. Finally, we discuss a handful of emerging issues that will potentially affect co-development and joint commercialization agreements.

2. Structuring Co-development and Co-Marketing Agreements

In co-marketing and co-development agreements there are a number of structural agreements that impact the rights and obligations of the parties. These issues tend to have a major impact on the type of relationship, the potential economic benefits arising from them, the freedom and discretion that the parties enjoy under the agreement and the business strategies of the respective parties. Although this list is not comprehensive, the issues that we provide will be relevant to most joint marketing and co-development agreements.

(a) Scope of Licence/Product Rights

One critical issue arising in any type of agreement is the scope of technology and indications to which the agreement will apply. Any person with even a moderate amount of familiarity with licensing will be familiar with a number of these considerations such as whether the agreement to commercialize or co-market is exclusive or non-exclusive and to what territories or jurisdictions it applies. However, biotechnology agreements create a number of additional issues in the area of the scope of the product or technology rights:

- At the outset it must be determined whether the licence applies to genomic or genetic targets, proteins arising from those targets or biological agents such as antibodies.
- These agreements typically also attempt to limit the number of targets, therapeutic or diagnostic compounds that interact with such targets. For example, the agreements may state that the biotechnology company will give the large pharmaceutical company rights to a certain number of targets or compounds but any additional targets or compounds are treated differently or belong entirely to the biotech company. For example for additional targets or compounds, additional fees could be charged, royalties could arise or the parties may have options to obtain the rights to these additional targets and compounds.
- Typically marketing and development agreements are also limited by the indications or disease states against which targets and compounds can be exploited. For example, it is quite common to licence targets or compounds in relationship to cancer or inflammatory diseases. Often these common terms for disease states are ambiguous. For example, referring to inflammatory diseases, this could mean the clinical signs of inflammation which include redness, pain, heat, swelling or loss of function. It could also include specific inflammatory disease symptoms such as inflammation arising from infection, inflammation arising from osteoarthritis and rheumatoid arthritis or inflammation arising from autoimmune diseases. Finally, inflammation could refer to specific biological pathways that lead to inflammatory responses. These different definitions will lead to broader or narrower rights under the agreements.
- Another example of the type of issues that can arise when defining indications arises from diseases or syndromes that are relatively poorly defined and yet give

rise to drug prescribing activity. For example, pelvic inflammatory diseases often result in prescription of drugs when certain clinical factors are found in conjunction with certain patent risk factors. The prescription may be made even when the underlying etiology of the syndrome or illness is unknown. In certain circumstances this may lead to uncertainty or disputes as to whether an obligation arises for payment of royalties. By way of a final example, many cancers are mediated in different ways. For example, if one indication for use of a drug was breast cancer, the parties may wish to consider whether hormone receptor mediated cancer should be treated differently than non hormone receptor mediated cancers.

- People often assume that phrases such as “diagnostic” and “therapeutic” have well defined meanings. Most people understand that a diagnostic identifies a particular disease or predisposition to a disease. However, it is less certain whether parties would intend diagnostic to also include defining the prognosis or progress of a disease. Equally, it is unclear whether parties would necessarily want to use the word “diagnostic” to determine which of two or more treatment modalities should be used. The following sample definition of the term “diagnostic” illustrates this issue.

“DIAGNOSTIC” means any product or service that:

- (a) identifies patients having a particular disease or having a predisposition to a particular disease, and/or
- (b) defines the prognosis or monitors the progress of any disease in a patient and/or
- (c) is used to select between two (2) or more therapeutic or prophylactic regimens, wherein at least one such therapeutic or prophylactic regimen involves a compound that could be used to treat and/or prevent a disease, and where the selected regimen is determined, based on the use of such product or service, to be the most effective and/or to be the most safe for a patient.

Similarly, when defining a therapeutic, it is unclear whether this would include compounds, protein or other active or biologic materials that had palliative effect.

(b) Dropped Targets

Another significant structural issue that parties must determine is under what circumstances a target or compound will no longer be the subject of the co-development and co-marketing agreements. For example, often the parties will perform some development work on a compound and then one of the parties loses interest, or perhaps both parties will lose interest. At that time, one or the other of the parties may want either an option or an absolute right to deal with the dropped targets as they wish by, for example, carrying on development on their own or having the right to carry out joint development with a third party. Licensees or large pharmaceutical companies typically want to hold on to rights relating to potentially dropped targets as long as possible. On

the other hand, when single targets could lead to blockbuster drugs, biotech companies typically want to regain rights to dropped targets as soon as possible. The parties need to give adequate consideration to the criteria for dropping a target, the process by which potentially dropped targets can be identified and evaluated, and the economics behind reclaiming dropped targets.

(c) Reciprocity

One important issue arising in co-development agreements is whether there will be some parity between the parties in their ability to exploit or commercialize targets or compounds that are identified and developed during the joint activities. For example, a research program might have a goal of identifying half a dozen lead compounds arising from two genomic targets for a particular set of indications. If the agreement is reciprocal one of the parties might have rights to exploit half the identified compounds and the other party might have the rights to exploit the other half of the compounds. If this is the case, then perhaps the parties will select compounds out of a pool of candidates through some sort of alternating selection mechanism. On the other hand, if the agreement is not reciprocal, one party, typically a large pharmaceutical company, will have rights to exploit all compounds arising out of the research program.

Analogously, in co-marketing agreements where there is reciprocity, a large pharmaceutical company may give the biotech company the rights to co-market existing products of the large pharmaceutical company. The great advantage and benefit of this is that often pharmaceutical sales representatives who make calls on doctors and other health care professionals find it much more efficient to attempt to provide information on two or three drugs in one sales call instead of just providing information about, or attempting to sell, only one drug.

Another aspect of reciprocity is whether research and development tasks will be carried out primarily by one party. There are hybrid arrangements as well, for example, the small biotech company might carry out all the research and development activities and obtain regulatory approval and then hand the compound off to the large pharmaceutical company when it is ready for marketing. This is a rather extreme example as in most cases the large pharmaceutical company will want to have a significant role in the regulatory approval process.

In another extreme example, the parties agree to work together jointly on all activities and contribute equally to the costs and resources required. In this sort of situation the parties typically agree to both provide a set level of resources, be that dollar or full time equivalent of personnel. The activities carried out can be either determined in advance by way of a pre-determined project plan, or can be determined from time to time by some sort of a joint planning committee.

Finally, another aspect of reciprocity is that sometimes the parties will cross-licence intellectual property rights to each other. Some issues surrounding intellectual property are discussed later in this paper.

(d) Program Success Criteria/Project Definition

One critical aspect of any sort of co-development agreement is the extent to which the criteria of project success or the criteria for determining whether a target or candidate can move to the next phase of the project are determined in advance and determined by objective criteria. For example, in situations where a large pharmaceutical company has a great deal of negotiating power, it may take the position that whether or not a research compound or target is adequate or suitable and whether or not the project should move to a subsequent stage will be decided in its sole discretion. At the other extreme are situations where criteria for successful completion of the project as a whole or its phases is determined in advance by the parties according to written or measurable standards. For Example, validation may include:

- a. The target has been confirmed through genetic studies to be associated with disease states;
- b. A drugable target has been found, i.e. proteins or biological pathways associated with the genetic target have been found to be accessible to therapeutic compounds at various binding sites;
- c. The proteins or compounds associated with accessible binding target sites have passed some preliminary ADMET screening;
- d. The compound associated with the target have passed various biology screens;
- e. The compound has been proven to work in either in vitro or in vivo models.

Probably the most common situation is a balance between these two extreme positions wherein some success factors are set out at a reasonable level of specificity, but the parties retain some discretion to determine whether the project is being successfully completed.

A related issue is the extent to which the research program that the parties will carry out is defined in advance. In some agreements a well defined research program is determined in advance by the parties. Any change to this program requires the mutual consent of the parties. Where the parties are less balanced in power, or where it is much more difficult to determine with certainty the research program that has to be taken out, it may be more common for the parties to agree to contribute a certain level of resources, but the activities that will be carried out with those resources will be determined from time to time according to the governance provisions of the agreement. At an extreme end of the spectrum, one party agrees to do work under the control of the other party. For example, the small biotech company may agree to carry out various research and development activities, the money for this to be provided by the large pharmaceutical company, with the large pharmaceutical company also specifying what activities will be carried out and when.

(e) Incentives

Under any co-marketing or co-development agreement, the parties should give consideration to whether or not it is worthwhile to create incentives to effectively carry out the activities under the agreements. There are two broad types of incentives that can be considered. The first are incentives for one party, typically the biotech company, to more quickly or effectively carry out its activities. These could include increases in royalty rates or milestone payments if deliverables under a development agreement, such as validated targets or compounds, are delivered more quickly than are required under the development agreement. It could also include increases in royalty rates or milestone payments where regulatory approval is obtained more quickly or where the licensee, such as the large pharmaceutical company, exploits a greater number of compounds.

Another important type of incentive that is being seen in recent deals is for research and development by biotech companies to be funded by way of forgivable loans. When the pharmaceutical company decides it wants to exercise its options to acquire various rights in relation to validated targets or compounds, then loans that it had previously made to the biotech company to fund the research and development are forgiven in whole or in part.

There is another type of incentive that should be considered. This is the equal treatment of results of the co-development and co-marketing programs with internal activities by the large pharmaceutical company. One problem that is frequently seen in co-development agreements (or in any sort of licensing in of technology by large pharmaceutical companies) is that the licensed in or co-developed technology is subject to much more rigorous review than are activities occurring or originating within the large company. In some cases this may be a reasonable approach because the biotechnology company may have omitted various steps in its research and development program due to time or budgetary constraints. However, there is also a sense that some people within large pharmaceutical companies may try to increase recognition for internal projects by unduly criticizing external projects. Useful incentives to resolve this sort of situation would include ensuring that internal personnel and managers of the large pharmaceutical company get rewarded for the accomplishments of the co-development or co-marketing project as if the project had been done entirely within the large pharmaceutical company. In other words, there is no distinction made between internal and external projects.

Finally the parties will want to give thought to other structural issues such as whether milestone payments or other fees are creditable or non creditable against later royalties. As well, they will want to consider whether upfront or milestone payments are going to be refundable in any circumstances.

(f) Options

One of the most important tools in structuring a biotechnology transaction is granting the parties options to receive various rights relating to the technology and the products created under the agreements. There are four major types of options to consider when structuring these types of agreements:

- (i) Options to acquire technology. Very frequently the large pharmaceutical company will agree to fund research and development relating to validating and obtaining regulatory approval in relation to targets and compounds. When the biotech company also contributes a portion of the research and development costs, then it is common that the large pharmaceutical company only obtains comprehensive rights to the technology after exercising an option and paying an option fee which usually would consist of milestone payments, royalties and reimbursement of the biotechnology company for its research and development costs. It is also quite common in this type of agreement that the large pharmaceutical company has a number of points during the research and development cycle at which it can exercise these options. However, the longer it waits to exercise options, the more it must pay. This makes economic sense since the longer the pharmaceutical company waits to exercise its option, the more cost and risk the biotech company has incurred.
- (ii) Options to Acquire Dropped Technology. A second important type of option is an option to acquire sole rights to targets and compounds that are no longer of joint interest to the parties. For example, after research and development has occurred for a period of time, one or the other parties may decide that they are no longer interested in pursuing the program or a portion of it. The other party may still be interested in the technology and doesn't want the research and commercialization related to the target or compound to grind to a halt merely because the parties have different views. In these sort of situations it is quite common for the parties to grant each other an option that if they lose interest and no longer wish to contribute to the research and development program that the other party has the option of obtaining a controlling and exclusive interest in the technology. Often this is accomplished by paying the costs incurred to date and agreeing to pay a nominal royalty relating to the re-acquired property.
- (iii) Evaluation Options. A third important type of option to consider is an option simply to view or get to know the technology. This is often referred to as an evaluation licence, a "rent to test" agreement or a "rent to buy" agreement. In these agreements a party, typically a large pharmaceutical company, is allowed to receive research results and possibly perform tests on targets or compounds of interest for a period of time. At the end of the evaluation period, they must then elect whether to enter into a more comprehensive co-development and co-marketing agreement or they relinquish all their rights. One problem inherent in this type of evaluation agreement is that it is possible for the large pharmaceutical company to try to acquire a blocking patent position in relation to the technology it is evaluating. Where the biotech company has enough negotiation strength, it will want to obtain an agreement that any intellectual property created during the evaluation period relating to the evaluated targets and compounds will become the property of the biotech company unless a development or marketing agreement is entered into later.

- (iv) Option to Acquire Improvements/Additional Compounds. The last type of option that should always be considered in these types of agreements is the option to acquire additional compounds and targets or to acquire improvements relating to compounds and targets. These types of options are important for a number of reasons. First, sometimes the true economic benefit relating to new biotechnology or pharmaceutical products arises from having a cluster of two, three or four products so that a company, typically the large pharmaceutical company, can claim comprehensive coverage of a certain clinical or product area. Secondly because of the risks and uncertainties arising from this type of research, quite often the first or main compound fails to produce the desired or expected results and the program is only successful because it was possible to continue development and commercialization on second or alternative targets, compounds or products. Finally, creating and sustaining blockbuster products often involves obtaining drug, line and indication extensions. The licensee of the technology will usually want to have certain rights and options to obtain intellectual property that would be required in order to create such line and indication extensions.

Next, this paper goes on to consider more specific clauses that are often found in co-development and co-marketing agreements.

3. Sample Provisions

(a) Introductions and Disclaimers

In this section I will provide a number of sample clauses that address some of the key issues that arise in co-marketing and co-development agreements. A few disclaimers are in order:

1. These sample clauses are largely drawn from actual transactions. As such, they reflect a certain set of facts as well as certain bargaining strengths between the parties. In many cases they represent the final position that was arrived at between the parties. As such, it would be disadvantageous in negotiations to use these sample clauses as stating positions. These clauses may give away too little or too much and leave little room for compromise.
2. A further problem with these sample clauses is that generally they have been crafted in the context of agreements between well informed parties. As everyone is aware, where one party has superior bargaining power or relatively superior counsel, it is possible to draft a clause that would be significantly more one-sided.
3. In certain circumstances the sample clause that is provided may be far more than the client requires. It may address issues that are not consequential in the context of the transaction or may propose mechanisms or procedures which in the context of the transaction would be far too costly or cumbersome. This type of legal drafting rarely assists clients. As well, when clauses are inserted that address

inconsequential risks there is always the risk that the solicitor who uses these clauses will not understand a reasonable fall back position relating to these issues.

4. Another consideration in these sample clauses is that often effective use of precedent materials requires a fairly thorough understanding of the legal doctrines that may be at play in the application or implementation of the precedent.

(b) Governance and Control of Joint Activities

One of the most critical aspects of any co-development or co-marketing agreement is the clauses and provisions that will set out how the joint activities will be controlled. This is particularly relevant in many biotechnology arrangements where the time required to take a new product or compound from the earliest stages of development to the marketplace often exceeds ten years. As well, there is often a great deal of scientific and project management uncertainty as to the particular tasks that must be carried out and the priority of various activities.

The most common form of arrangement is to establish a committee or series of committees to deal with the governance of the collaborative activities. For example, it is quite common to establish an executive committee (which is often referred to as a management committee or steering committee) and a number of sub-committees which may include a research committee and a marketing committee. The responsibilities of these committees and the areas over which they are entitled to make decisions are usually set out in some detail. This serves to constrain the discretion of the parties because then it is very clear that certain types of decisions must be brought before this committee and the decisions can only be made according to the decision making rules (for example membership, quorum, voting and dispute resolution) that has been established for the committee. Another very common aspect of these types of governance procedures is that where a sub-committee is unable to reach a decision or where a decision of a sub-committee is disputed by someone on the committee, there are rights to appeal the disputed decision to more senior committees. In practice this seems to be of significant value as it encourages a second look at disputed matters, and relies on the fact that the more senior committees are often staffed with the more senior personnel of the respective parties. The prospect of having one's decision reviewed by a more senior person has a number of beneficial effects. First, if the more junior person on the sub-committee is taking an intransigent or illogical position, they may moderate this position if their non-constructive approach is subject to review by a more senior person within their own organization. Second, where the sub-committee is asking them to take a risky decision, it may be easier to refer that issue to the more senior committee where a more senior person may have greater authority to make, or experience in making, such a decision.

Within these committees usually some form of unanimous decision making is common. Both parties typically place the same number of persons on the committee and all decisions by the committee either require an unanimous approval by the committee or approval including at least one person from each party. Alternatively, the committee's governance provisions may grant more decision making authority to one party, for example by having voting on committee by a majority vote and giving one party more positions on the committee. In these sorts of circumstances it may be possible that

certain types of decisions get explicitly excluded from the decision making of the committee.

Here is a sample clause that sets out a fairly extensive set of responsibilities for a joint steering or management committee for a co-development and co-marketing arrangement. It can be noted that this clause deals with the power to resolve matters which the sub-committees are unable to resolve. It also gives the joint steering committee sole responsibility for the listed tasks and activities.

The Parties shall establish a Joint Steering Committee which shall have as its overall purpose the development, implementation and management of commercial planning activities and research and development programs with respect to BiotechCo Licensed Products, each consistent with the other. The Joint Steering Committee shall have such subcommittees (in addition to the Marketing Subcommittee and the Development Subcommittee as the Parties or the Joint Steering Committee may mutually agree from time to time hereafter. The Joint Steering Committee shall consist of a number of from two (2) to ten (10) representatives from each Party drawn from among such Party's senior managers.

Within thirty (30) days after the Effective Date each Party shall appoint two (2) members to the Joint Steering Committee. Either Party may replace one or more of its members on the Joint Steering Committee by providing notice to the other Party. The Joint Steering Committee shall, in addition to such other responsibilities as are assigned to it herein, review the activities of the Marketing Subcommittee, the Development Subcommittee, and any other subcommittees formed from time to time, and seek to resolve any matter upon which any such subcommittee is unable to make a decision, except as otherwise provided herein. Among its other responsibilities, but without limitation, the Joint Steering Committee solely shall be responsible for:

- (a) approving any proposed Commercialization Plan and Budget, submitted to it by the Marketing Subcommittee or the Development Subcommittee,
- (b) approving any proposed material amendment to any Commercialization Plan and Budget and Development Plan and Budget submitted to it by the Marketing Subcommittee or the Development Subcommittee,
- (c) managing the BiotechCo Licensed Product life cycle and intellectual property protection, and identifying the extent to which any Intellectual Work Product likely to result from development activities being considered by the Joint Steering Committee would be subject to ownership or Control by a Third Party;
- (d) approving any and all prices for BiotechCo Licensed Product throughout the Territory proposed by the Marketing Subcommittee including any and all ranges of discount amounts within which the Marketing Subcommittee shall have discretion to operate, and any

material changes to the PharmaCo Trade Policy affecting the treatment of BiotechCo Licensed Product returns and refunds,

(e) approving the list of BiotechCo Licensed Product Target Prescribers, the allocation of Details to be performed by each Party among BiotechCo Licensed Product Target Prescribers, and any material changes to such allocation,

(f) reviewing and approving any plans and budgets prepared jointly by the Marketing Subcommittee and the Development Subcommittee for any Phase 3b Studies, Phase 4 Studies, or health outcome studies for BiotechCo Licensed Product,

(g) approving any study protocol and any material amendment thereto for any phase 3 study (including Phase 3a Studies and Phase 3b Studies) for the Second Indication;

(h) for any Additional Indication, approving any clinical study protocol, and material amendments thereto for phase 2 or phase 3 study activities performed under this Agreement,

(i) for any Additional Indication, approving any INDs and NDAs to be submitted to Regulatory Authority and any material labeling changes to any BiotechCo Licensed Product.

By way of example, the sub-committees may also each have detailed lists of responsibilities. Again the main purpose in this is to force the parties to make certain decisions according to the governance procedures under the agreements and not give them the opportunity to argue that certain decisions are within their discretion or not covered under the terms of the agreement.

The Marketing Subcommittee shall:

(a) prepare, and review on a quarterly basis, the Commercialization Plan and Budget, subject to the final approval of the Commercialization Plan and Budget by the Joint Steering Committee ; and

(b) subject to, and within the constraints of, any approved Commercialization Plan and Budget:

(i) oversee the implementation of the Commercialization Plan and Budget, and ensure that each Party executes its responsibilities described in such Commercialization Plan and Budget;

(ii) develop and discuss strategies for the Detailing and marketing of BiotechCo Licensed Products in the Territory, including allocation of responsibility for marketing activities, and support through professional education;

(iii) in collaboration with the Development Subcommittee, deciding whether to perform, and then preparing any plans and budgets for any health outcome studies for BiotechCo Licensed Product;

(iv) propose to the Joint Steering Committee the Launch Date , and the date of launch for any subsequent BiotechCo Licensed Products;

(v) propose to the Joint Steering Committee the price for BiotechCo Licensed Product throughout the territory and any and all ranges of discount amounts within which the Marketing Subcommittee shall have discretion to operate, and any material changes to the PharmaCo Trade Policy affecting the treatment of BiotechCo Product returns and refunds, and establish the conditions of distribution and sale of BiotechCo Licensed Product;

(vi) propose to the Joint Steering Committee the list of BiotechCo Product Target Prescribers and the allocation of Details to be performed by each Party among BiotechCo Licensed Product Target Prescribers, or material changes to such allocations previously approved by the Joint Steering Committee;

(vii) review progress of commercialization activities against the current Commercialization Plan and Budget;

(viii) review the rate of spending on commercialization activities against the budget for such activities in the Commercialization Plan and Budget;

(ix) propose the long term forecasts of BiotechCo Licensed Product needs, for approval by the Joint Steering Committee;

(x) prepare short term forecasts of BiotechCo Licensed Product;

(xi) compare actual BiotechCo Licensed Product sales against sales forecasts and targets set out in the Commercialization Plan and Budget;

(xii) consider, and propose to the Joint Steering Committee, potential amendments to the Commercialization Plan and Budget;

(xiii) establish working groups to implement the Commercialization Plan and Budget;

(xiv) present the results of commercialization efforts to the Joint Steering Committee;

(xv) undertake all other activities necessary to manage the marketing and sale of BiotechCo Product in the Territory;

(xvi) any other duties that are delegated to the Marketing Subcommittee by the Joint Steering Committee; and

(c) review and comment on the semi-annual report on the Parties' commercialization activities under this Agreement prepared by BiotechCo.

As stated above, another important governance technique is to ensure that the parties commit to a certain level of funding or resource contribution to the joint activities. A sample clause that would deal with these issues is as follows:

Initial Commercialization Plan and Budget. The Marketing Subcommittee shall propose to the Joint Steering Committee a Commercialization Plan and Budget for all marketing, sales and educational activities up to the Launch Date within three months after the Effective Date (the "Initial Commercialization Plan and Budget"). The Initial Commercialization Plan and Budget adopted by the Joint Steering Committee shall provide for minimum funding by the Parties of promotional activities, as follows:

(a) at least X U.S. dollars (U.S. \$X) from the Effective Date through the end of Calendar Year A,

(b) at least Y U.S. dollars (U.S. \$Y) from Calendar Year B until Calendar Year C,

(c) at least Z U.S. dollars (U.S. \$Z) from Calendar Year D until the date Calendar Year E.

If the Initial Commercialization Plan and Budget is not finalized in accordance with this Section, then the amounts described herein shall constitute such budget.

Typically where essential decision making is required, if the most senior committee, such as the joint steering committee is unable to resolve the matter or make a decision the matter is then turned over to the dispute resolution provisions under the agreement which provide for litigation, arbitration, mediation or some combination of these.

(c) Measuring the Contribution of the Parties

Typically co-development and co-marketing agreements involve both parties making commitments to contribute resources. An important consideration is to create mechanisms so that the parties assure themselves that the relative contributions are correct, fair and accurate. One general clause that addresses this sort of issue is set out below:

If either Party believes that there is a material imbalance in resources devoted to, or participation by the Parties in, the Research Program, such Party may submit the matter to the Joint Research Committee in writing. Taking into account historical and prospective participation and resource devotion of the Parties during the current Contract Year and the immediately following Contract Year, the Joint Research Committee shall take such steps as may be reasonably necessary to ensure substantial equality in resources devoted and participation by the Parties in the Research Program.

The parties may also want to create certain inspection and audit rights related to the level of contribution. A sample clause is as follows:

At the request of a Party, the other Party shall permit an independent, certified accountant appointed by the requesting Party, at reasonable times and upon reasonable notice but no more than once per year, to examine, at the sole cost of the requesting Party, the records of the other Party to verify the accuracy of any reports submitted by the other Party to the Joint Research Committee regarding the level of resources devoted to the Research Program by such Party.

As a related issue, the parties may want to make audit easier by requiring that resources and costs incurred by the project are accounted for separately. A clause dealing with this is set out below:

Each Party shall be responsible and pay for all Development Expenses incurred in performing its obligations in connection with any development activities under the Development Plan and Budget. Each Party shall charge all such expenses so incurred to a separate account created by it on its books and records solely for the purpose of tracking Development Expenses, identifying all Development Expenses by the BiotechCo Licensed Product and indication being developed (the "Development Account").

It is quite common in co-marketing and co-development agreements to allocate full time equivalent (FTE) personnel. When this is done it may be desirable to address some of the following issues:

- At what level of detail should each FTE activities be tracked?
- Can a party allocate overhead, benefit or severance related expenses related to FTEs to the development project?
- To what extent are personnel records related to each FTE made available to the other party?

(d) Information Rights

Parties to co-development and co-marketing agreements frequently encounter problems when they have different expectations about the amount and type of information that they will disclose to each other regarding the activities carried out under the agreement.

There have been some notable cases over the past ten years where parties have paid tens or even hundreds of millions of dollars for co-development and co-marketing activities and yet the other party takes the position that very little information has to be disclosed relating to these activities. The parties may want to consider a general clause relating to exchange of information under a development agreement such as the following:

BiotechCo will promptly make available and disclose to PharmaCo such information regarding the sequence, design, synthesis, screening development, approval, commercialization and marketing of the BiotechCo. Licensed Products arising from the Collaboration as set forth in the Collaborative Research Plan. All discoveries or inventions made in the course of the Collaboration by a Party will be promptly disclosed to the other Party. At a Party's request, the other Party will provide written reports of any studies performed by such other Party as part of the Collaboration required to support regulatory submissions relating to Products to be made by such first Party or its Sublicensees and will allow such first Party and its Sublicensees to use the data included in such reports to support such submissions. The Parties are encouraged to communicate often by telephone, electronic mail or other mechanisms to keep each Party fully advised of the activities being carried out by a Party under the Collaboration.

The parties should also consider whether they want rights to visit and inspect the facilities where the collaboration is occurring. If they do the following type of clause may be desirable:

Representatives of PharmaCo and BiotechCo may, upon reasonable notice during normal business hours,

(a) visit the facilities where the Collaboration is being conducted, including activities carried out by Third Parties,

(b) consult informally, during such visits and by telephone, with personnel for the other Party performing work on the Collaboration, and

(c) with the other Party's prior approval, which approval shall not be unreasonably withheld, visit the sites of any experiments or tests being conducted by, or on behalf of, such other Party in connection with the Collaboration. On such visits, an employee of the Party being visited shall accompany the employee(s) of the visiting Party. If requested by a Party, the other Party shall cause appropriate individuals working on the Collaboration to be reasonably available for meetings at times and places reasonably convenient to the Party subject to such request.

One important area where information should be shared is in relation to securing regulatory approval for therapeutics and diagnostics. The following set of provisions deal with regulatory strategy, regulatory information, meeting with regulatory authorities and reporting of adverse drug experiences.

7.1 Information Rights; Regulatory Matters – Communication with Regulatory Authorities

7.1.1 General. BiotechCo shall consult with PharmaCo through the Development Subcommittee (DSC) on the regulatory strategy to be pursued for BiotechCo Licensed Products. BiotechCo shall be solely responsible for maintaining and seeking in its own name Regulatory Approvals for BiotechCo Licensed Product, including all NDAs and all additional or supplemental Regulatory Approvals, provided any filings for Regulatory Approvals submitted after the Effective Date are not inconsistent with the decisions of the Joint Steering Committee or its subcommittees. BiotechCo shall be solely responsible for filing all reports required to be filed in order to maintain any Regulatory Approvals granted for BiotechCo Licensed Product, including, without limitation, Adverse Drug Experience reports. BiotechCo shall not make any submissions to any Regulatory Authority concerning an NDA that are intended to materially change or modify the label or labeling for, or the indication of BiotechCo Licensed Product without first notifying and obtaining the input of the DSC. BiotechCo shall not make any material submissions to any Regulatory Authority of an NDA, or concerning an NDA, for BiotechCo Product for an Other Indication without the approval of the Joint Steering Committee. At least thirty (30) days before making any material submission to any Regulatory Authority of an NDA, or concerning any NDA, for BiotechCo Licensed Product for the Second Indication or any Additional Indication, BiotechCo shall provide the Joint Steering Committee with a copy of such submission, and BiotechCo shall adopt reasonable suggestions made by the Joint Steering Committee to the extent feasible. PharmaCo shall cooperate with BiotechCo as needed in preparing and filing all such reports and, upon BiotechCo's request, provide BiotechCo with any information in PharmaCo's possession or control that BiotechCo reasonably deems to be relevant to any such reports.

7.1.2 BiotechCo Notification of Significant Regulatory Information.

BiotechCo shall promptly notify the PharmaCo members of the Development Subcommittee as soon as material information and data generated in the course of the development program become available to BiotechCo. BiotechCo will promptly provide the members of the Development Subcommittee with all such material information and data in order to evaluate this progress in the development program.

7.1.3 PharmaCo Meeting Attendance.

PharmaCo shall have the right to have up to three (3) of its representatives attend all meetings and conferences and participate in all material telephone discussions with any Regulatory Authority in the Territory concerning BiotechCo Licensed Products. BiotechCo shall promptly provide PharmaCo's members on the Development Subcommittee with copies of all correspondence between BiotechCo and a Regulatory Authority regarding BiotechCo

Licensed Products, or regarding the activities under this Agreement at least seven (7) days before the submission of such correspondence, to the extent reasonably feasible. BiotechCo shall adopt all reasonable material suggestions and recommendations of PharmaCo concerning such correspondence, to the extent feasible.

7.1.4 Inspections & Inquiries.

If either Party or any of their respective Affiliates is inspected by or receives inquiries from a Regulatory Authority regarding activities under this Agreement with regard to BiotechCo Licensed Products, such Party or the applicable Affiliate shall promptly notify the other Party, but in no event no more than forty-eight (48) hours after such inspection or inquiry. The inspected Party or its Affiliate shall provide the other Party with a written report of any such inspection, noting with specificity any record or document reviewed by the regulatory inspector. When a copy of a document or record is supplied to the inspector on request, that fact will be noted in the report. The inspected Party or its Affiliate shall keep copies of each of these records or documents in a separate inspection file and, on the other Party's request, will provide such other Party with copies of any or all of these documents or records.

7.1.5 PharmaCo Communications with Regulatory Authorities.

If PharmaCo reasonably concludes, after consultation with its regulatory counsel, that PharmaCo must communicate with a Regulatory Authority regarding PharmaCo's activities under this Agreement, then PharmaCo shall so advise BiotechCo and provide BiotechCo with copies of all correspondence between PharmaCo and the Regulatory Authority. PharmaCo shall provide BiotechCo with copies of all correspondence, documents and materials received from a Regulatory Authority concerning BiotechCo Licensed Products or any activities under this Agreement. PharmaCo shall provide BiotechCo with copies of any proposed correspondence to a Regulatory Authority that relates to BiotechCo Licensed Products, or any activities under this Agreement at least seven days before the submission of such correspondence. PharmaCo shall adopt all reasonable suggestions and recommendations of BiotechCo concerning any meeting or written or oral communication with such Regulatory Authority.

7.4.1 Notification of Parties of Adverse Drug Experiences

7.4.1 Notification of Parties.

(a) Serious Adverse Drug Experiences . Each Party shall notify the other of any Serious Adverse Drug Experience within forty-eight (48) hours of the time such Serious Adverse Drug Experience becomes known to such Party or any of its Affiliates, with written confirmation of such notification no more than forty-eight (48) hours later.

(b) Non-Serious Adverse Drug Experiences . Each Party shall notify the other Party in writing of any Non-Serious Adverse Drug Experience within ten (10) days after the end of any Calendar Quarter, listing the Non-Serious Adverse Drug Experience that become known to such Party or any of its Affiliates.

(c) Complaints. PharmaCo shall refer any complaints, including medical complaints, that it receives concerning any BiotechCo Licensed Product to BiotechCo within ninety-six (96) hours of receiving such complaint; provided that all complaints concerning suspected or actual BiotechCo Licensed Product tampering, contamination or any BiotechCo Licensed Product that is out-of-specification shall be delivered within forty-eight (48) hours of receiving such Complaint.

7.4.3 Regulatory Reporting

BiotechCo shall be responsible for making all reports to any Regulatory Authority regarding Adverse Drug Experiences.

7.4.4. Disclosure of Adverse Drug Experiences

7.4.4 Except as required by applicable Laws, PharmaCo shall not disclose any information concerning any Adverse Drug Experience or any complaint concerning any BiotechCo Licensed Product to any Third Party without the prior consent of BiotechCo. BiotechCo shall be solely responsible for determining whether any complaint or Adverse Drug Experience must be reported to any Regulatory Authority and to provide such notification in compliance with applicable Laws.

(e) Personnel

The parties may often wish to consider whether certain key personnel of either party are essential for the success of the project. If the BiotechCo personnel are critical, the following clause may be appropriate:

During the Collaboration Term, BiotechCo shall inform PharmaCo if [key named persons] leave the employ of BiotechCo . In such case, PharmaCo shall have the right to suggest replacements and interview any potential replacement in order to provide feedback to BiotechCo regarding any such potential replacement, but, for purposes of clarification, PharmaCo shall not have the right to terminate this Agreement or the Collaboration as a result of the events described in this Section.

Where the large pharmaceutical company wants to create greater incentives for the BiotechCo to retain personnel it may want to have the following type of clause:

Where more than half of the following persons [named key persons] are no longer actively involved in the project, then PharmaCo shall have a right to terminate this agreement.

Although this type of clause creates many incentives for the BiotechCo to retain key personnel, there are many problems:

- How will the clause operate if personnel go on maternity leave or become sick or disabled?
- How will the clause operate if PharmaCo requests that people be removed from the project team?
- How will the clause operate if PharmaCo hires key personnel away from BiotechCo?

Another key issue that the parties should consider is the extent to which sub-contracting is permitted. Quite often parties will not want to allow sub-contractors to carry out the obligations of the parties because of the potential for contracting to potential competitors, or for concerns about confidentiality or expertise of the sub-contractor. In these situations, the following clause may be appropriate:

Subcontracting. Except to the extent approved by the Research Sub-Committee or as otherwise expressly permitted in the Collaborative Research Plan, neither Party shall subcontract to a Third Party any portion of the activities assigned to it under the Collaborative Research Plan, other than through the use of on site contract employees. To the extent such subcontracting is approved, prior to engaging a Third Party, BiotechCo or PharmaCo, as applicable, shall first obtain a written agreement with such Third Party containing appropriate confidentiality and non-use provisions as determined by the Joint Steering Committee and written assignments to BiotechCo or PharmaCo, as applicable, of all Patent Rights and Know-How that such subcontractors may develop by reason of work performed under such contract. Moreover, any Third Party subcontractor shall be required to perform its services in accordance with any applicable generally accepted professional standards as well as standards designated by the Joint Research Sub-Committee (if any) and with any applicable codes, rules and regulations.

In relation to sub-contracting there are further issues that are worth considering:

- Do parties have the right to audit proposed sub-contractors or existing sub-contractors to determine the standard of performance of their work?
- Are any prohibitions on sub-contracting waived for individual clinical sites or contractual arrangements of small financial magnitude?
- If sub-contracting is generally permitted, is it nevertheless prevented if sub-contracting is done by listed persons that might be in competition with one or the other of the parties?

(f) Intellectual Property Rights

Issues surrounding intellectual property rights arising from co-development or co-marketing arrangements are both critical and complex. The parties are concerned that all required intellectual property rights have been contributed or licensed into the joint venture to allow the contemplated activities to be carried out. Each party is also concerned that they not allow the other party to obtain any sort of blocking patents in relation to the co-developed or co-marketed technologies. As well, when parties bring research tools or other “background” intellectual property rights into the co-development it may be desirable to grant cross-licenses to such intellectual property rights.

The following sample clause provides an example about licenses that a biotech company might grant to a larger pharmaceutical company in order to address the issue of jointly developed technology, background IPRs and blocking patents:

8.1 Licenses to PharmaCo

8.1.1 RESEARCH LICENSES. Subject to the terms and conditions of this Agreement, BiotechCo hereby grants to PharmaCo:

(a) a co-exclusive (with BiotechCo), nonsublicensable, royalty free license during the Collaboration Term under the BiotechCo Collaboration Technology **[technology developed by BiotechCo during the Collaboration under the Agreement]** solely to the extent necessary or appropriate to carry out PharmaCo’s responsibilities under the Collaborative Research Plan;

(b) a non-exclusive, nonsublicensable, royalty free license, under the BiotechCo Technology **[i.e. background technology]** solely to the extent necessary or appropriate to carry out PharmaCo’s responsibilities under the Collaborative Research Plan; and

(c) an exclusive, nonsublicensable, royalty free license under the BiotechCo Blocking Patents:

8.1.2 PRODUCT LICENSES. Subject to the terms and conditions of this Agreement, BiotechCo hereby grants to PharmaCo

(i) an exclusive license, including the right to sublicense, under the BiotechCo Blocking Patents to make, use and sell the BiotechCo Licensed Products, and

(ii) a non-exclusive license, including the right to sublicense, under the BiotechCo Collaboration Technology to make, use, import, sell and offer to sell BiotechCo Licensed Products. Such licenses shall be royalty-bearing as expressly provided by this Agreement.

A few comments can be made about this draft clause:

- Clearly it may be desirable to have a reciprocal licence back in respect of research and products from the pharmaceutical company to the biotech company.

- One issue that this clause does not address is the freedom the parties have to take collaboration technology (the technology created under the co-development agreement) and use this for other purposes.
- The clause does also not address the scope or definition of “blocking patents”. Blocking patents are patents owned by a party that could prevent making, using or selling or exploitation of the product or technology developed under the co-development or co-marketing agreement. Blocking patents could be specifically listed, they could be defined as any patent rights that would be infringed by making, using or selling the subject matter of the co-development or co-marketing agreement, or they could be even more broadly defined to include enabling technologies that might help market or co-develop technologies subject to the agreements.

Another important consideration relating to intellectual property in the pharmaceutical and biotech area is the ability to seek extended patent protection or patent term extension. This is available in certain jurisdictions as compensation for lengthy regulatory approval processes. An example of this type of clause follows:

12.7 Patent Term Extensions

12.7 The Parties shall cooperate with each other in gaining patent term extension wherever applicable to any product containing the licensed technology. The Party selling the product shall determine which patents shall be extended. All filings for such extension shall be made by the Party to whom the patent is assigned; PROVIDED, HOWEVER, that in the event that the Party to whom the patent is assigned elects not to file for an extension, such Party shall

- (i) inform the other Party of its intention not to file,
- (ii) grant the other Party the right to file for such extension, and
- (iii) cooperate as necessary to assist the other Party in filing such extension.

As mentioned earlier, joint ownership of trade secrets is quite complicated, uncertain under Canadian law, and should be explicitly addressed in a written agreement. To further address these issues, the parties may wish to both explicitly assign ownership in trade secret rights and have a residuals clause:

Nothing in this Agreement shall be considered to limit either Party’s right to utilize residuals. The term “residuals” shall mean general know-how and expertise gained during the performance under this Agreement, which are unintentionally retained in the unaided memories of those employees, agents or contractors of the Party that have been working with any Collaboration Technology without reference to any material which is written, stored in magnetic, electronic or physical form or otherwise fixed form, and expressly excluding any information or works protected by copyright or patent legislation.

Clearly any co-development and many co-marketing agreements will also contain extensive clauses relating to filing for intellectual property protection, prosecution, patent applications, and dealing with infringement by third parties and infringement of third party technologies. These types of clauses are outside the scope of this paper.

(g) Royalty Provisions

If the agreements contain an obligation to pay royalties based on the sales of the co-marketed or co-developed products and that royalty is based on net sales, a proper definition of net sales is required. The following clause shows a fairly standard definition of net sales:

"NET SALES" means the gross amount invoiced by Licensor, its Affiliates, or any Sublicensee thereof to unrelated Third Parties, excluding any Sublicensee, for the BiotechCo Licensed Product, less:

- (a) Trade, quantity and cash discounts allowed;
- (b) Commissions, discounts, refunds, rebates, chargebacks, retroactive price adjustments; and any other allowances which effectively reduce the net selling price;
- (c) Refunds or credits for actual Product returns;
- (d) Any tax imposed on the production, sale, delivery or use of the Product, including, without limitation, sales, use, excise or value added taxes;
- (e) Allowance for distribution expenses; and

Such amounts will be determined from the books and records of Licensor or sublicensee, maintained in accordance with Generally Accepted Accounting Principles or, in the case of sublicensees, such similar accounting principles, consistently applied.

Some important considerations that are applicable in a biotechnology context that should be considered are the following:

- If the drug delivery system has not been determined, should the cost of drug delivery systems be excluded from net sales?
- If royalties have to be paid to secure rights to blocking patents owned by third parties, should these royalties be deducted from net sales or alternatively perhaps could they be used to adjust the royalty rate payable. In both cases, should costs relating to drug delivery systems and the payment of costs for blocking patents be capped in any way?
- Should any non cash transfers of licensed product be deemed to be net sales? What should be excluded from deemed net sales, for example, free samples of the product, samples required for clinical trials, samples required for other

aspects of regulatory approval or samples required for validation of the manufacturing process?

- Another important issue arises when the licensed product is sold in combination with some other product. One possible approach to this is set out in the following clause:

In the event that the Product is sold as part of a Combination Product (where "Combination Product" means any pharmaceutical product which comprises the Product and other active compound(s) and/or ingredients), the Net Sales of the Product, for the purposes of determining royalty payments, will be determined by multiplying the Net Sales of the Combination Product (as defined in the standard Net Sales definition) by the fraction, $A / (A+B)$ where A is the weighted average sale price of the Product when sold separately in finished form, and B is the weighted average sale price of the other product(s) sold separately in finished form.

In the event that the weighted average sale price of the Product can be determined but the weighted average sale price of the other product(s) cannot be determined, Net Sales for purposes of determining royalty payments will be calculated by multiplying the Net Sales of the Combination Product by the fraction A / C where A is the weighted average sale price of the Product when sold separately in finished form and C is the weighted average selling price of the Combination Product. In the event that the weighted average sale price of the other product(s) can be determined but the weighted average sale price of the Product cannot be determined, Net Sales for purposes of determining royalty payments will be calculated by multiplying the Net Sales of the Combination Product by the following formula: one (1) minus B / C where B is the weighted average sale price of the other product(s) when sold separately in finished form and C is the weighted average selling price of the Combination Product.

In the event that the weighted average sale price of both the Product and the other product(s) in the Combination Product cannot be determined, the Net Sales of the Product will be negotiated by the parties in good faith. If the parties cannot reach agreement on the appropriate allocation, the Net Sales of the Product will be deemed to be equal to fifty percent (50%) of the Net Sales of the Combination Product.

The weighted average sale price for a Product, other product(s), or Combination Product will be calculated once each Calendar Year and such price will be used during all applicable royalty reporting periods for the entire following Calendar Year. When determining the weighted average sale price of a Product, other product(s), or Combination Product, the weighted average sale price will be calculated by dividing the sales dollars (translated into U.S. dollars) by the units of active ingredient sold during the twelve (12) months (or the number of months sold in a partial calendar year) of the preceding Calendar Year for the respective Product, other

product(s), or Combination Product. In the initial Calendar Year, a forecasted weighted average sale price will be used for the Product, other product(s), or Combination Product. Any over or under payment due to a difference between forecasted and actual weighted average sale prices will be paid or credited in the first royalty payment of the following Calendar Year.

4. Emerging Issues

In this section we discuss some issues that may have a significant impact on co-development and co-marketing agreements.

(a) Pharmacogenomics

With the advent and improvement of genomic technologies, it is possible to direct therapeutics towards sub-populations. This may have tremendous benefits for patients. For example, it may help improve the efficacy of therapeutics and help avoid adverse drug reactions. This is a significant problem in North America with over 100,000 deaths per year estimated to arise from adverse drug reactions. The possibility of reducing this death rate by the use of targeting sub-populations is very attractive. At the same time, targeting therapeutics at sub-populations may have a tremendous impact on the economics, risks and opportunities underlying co-marketing and co-development agreements. For example, targeting sub-populations may increase expenses required for regulatory approval substantially as more target populations need to go through clinical testing. At the same time, targeting of sub groups may reduce promotional expenses significantly as it will become much more apparent which patient population groups would benefit from using a particular therapy. Many large pharmaceutical companies object to targeting sub-populations because they, quite correctly, anticipate that this will reduce the number of blockbuster drugs which may decrease their overall profitability. It would be advisable that in preparation of any agreement issues surrounding sub-populations and pharmacogenomics be addressed, for example:

- The parties may want to explicitly have a provision stating that they will discuss the targeting of the sub-populations.
- At the present time it is uncertain whether it will be possible to obtain significant additional premium prices for products targeted at sub-populations. The parties may wish to consider that if such premiums are available, whether this will affect the economic terms of any agreement.
- The parties may wish to state that they agree that they will apply different economic models when products are produced for sub-populations, depending on the market potential of the sub-population, and costs associated with developing compounds for the sub-population. These differing economic models could impact contribution of resources, as well as milestone and royalty payments.

(b) Cost Control

It is uncertain if the United States will impose significant cost controls on pharmaceutical and biotechnology therapeutics and diagnostics. The parties may wish an adjustment clause in the event that government regulation drives down expected selling prices. Recently there have been increased efforts to encourage or compel pharmaceutical and biotechnology companies to provide their products to third world populations at significantly discounted amounts. The parties may wish to consider addressing the potential for this type of discounting in their agreements.

(c) Royalty Stacking

Biotechnology products may involve as many as six to ten different sets of patent rights. There may be royalties on compounds, drug delivery systems, research tools and on the genetic targets that the compounds arise from. It is difficult to co-ordinate agreements with these different patent owners as well as ensuring that when all the economic demands of these different owners are satisfied that the overall project will be economically viable. There are a number of issues that arise when addressing this prevalent problem:

- It is critical that any sort of biotechnology company understand its intellectual property position. As such, an essential element of any sort of due diligence is understanding the existence of blocking patents that exist or the requirement to obtain patent rights in enabling technology.
- The parties may want to adjust royalties (or deemed revenues) based on third party royalty on patent payments. There are a number of different approaches to this adjustment of royalties or revenue amounts. These can include capping the amounts that will be deducted as a result of payments to third parties for their patents or blocking or enabling technology. It is quite common in transactions to indicate that royalties can be reduced by as much as half to deal with blocking or enabling technology.
- If deductions are allowed relating to blocking or enabling technology, there are a number of questions and issues that must be addressed. Will a proper audit trail be created to indicate that payments were actually made to *bona fide* arms length third parties? How will accounting be made for cross licenses or when access to blocking or enabling technologies involve some form of non-cash consideration, debt or equity?

(d) Manufacturing Capabilities

In the early days of the biotechnology industry, it was thought that biotechnology products would be “silver bullets” and very small quantities of them would be required to create a large clinical effect. Unfortunately, this has not turned out to be true. Generally it has been found that milligram and not microgram quantities of biotechnology products are required for each patient per day. This means that it is critical for parties to enter co-development and co-marketing agreements to ensure that market demand for new products can be satisfied. Unfortunately there have been significant instances in the past few years where market demand for new products could not be satisfied. The parties

may wish to have contractual provisions that estimate, specify and warrant manufacturing capacity. The parties may also want to have the ability to adjust these estimations and specifications throughout the project. In other words, covenants relating to manufacturing capacity could be linked to options to proceed that occur at various phases of the project. It should also be noted that parties frequently forget to warrant or covenant the ability to produce products for testing and direct delivery design purposes.

(e) Drug Delivery Technologies

Effective commercialization of biotechnology products often requires good drug delivery systems. At present it is estimated that there are over 600 drug delivery technology companies that produce anything from molecular carriers of biotechnology products through to physical devices such as patches. A key issue to consider is how the cost of the drug delivery technology will affect the economics of the deal. For example, will the cost of drug delivery systems be deducted from the deemed revenues arising under the deal? Which party will bear the risk of uncertainty around the cost or availability of drug delivery technology?