BioCT common tools for european biotech

WP5 : Sharing Facilities

Deliverable 5.2:

Bridging the gap from preclinical to phase 1: general guidelines for biocluster's development – Report on clusters needs and selection of possible shared facilities

August 2010

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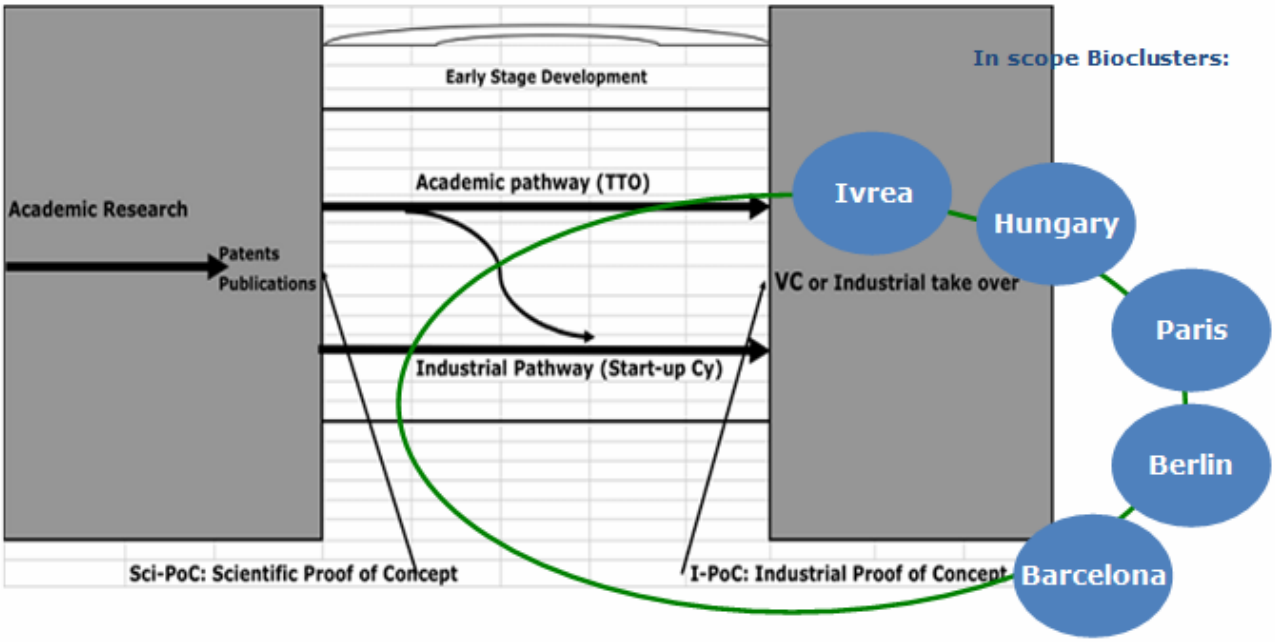
1. Project Summary

1.1 Overall Project Objectives

Objective of the Bio-CT project is to deliver a Join Action Plan (JAP) in which the different Bio-Regions of the Consortium - alongside and hopefully together with other additional Bio-Regions in future - will commit under sustainability conditions to open a good number of



Facilities and Services.

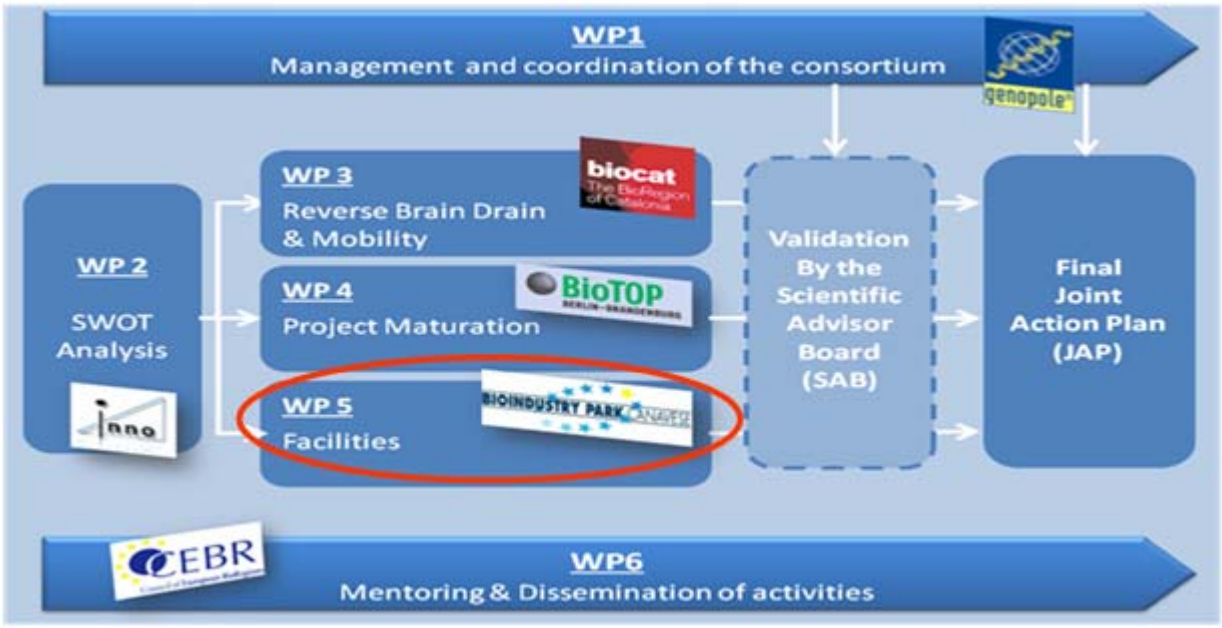
Such JAP will be studied in a limited area of the life Sciences: The Translational Medicine and for a specific stage of the companies' development: the I-PoC (Industrial Proof of Concept) stage, when companies need mostly to access said services and facilities.

The overall project is divided in 4 specific technical work packages:

- WP2 - SWOT Analysis of the mature research driven clusters: The SWOT analysis and competence mapping of the various clusters is the keystone of the project. It has been managed by a team composed of inno-TSD consultants, who have more than 15 years of experience in running such analyses, and has followed a bottom-up and homogeneous methodology. The results of this comprehensive analysis have been colleted and published through the deliverables of this WP at the beginning of 2010.

- WP3 - Fostering reverse brain drain to European countries and improving inter-sectorial and cross-regional mobility. The WP3 will analyse different barriers in the EC for reversing brain drain including those affecting mobility between academia and industry, and existing schemes to overcome them. The WP3 aim is to create a tool, operated jointly, for detecting confirmed Biotech researchers, that would be candidates for new positions within the project consortium, and financing any form of salaries for them.

- WP4 - Development of technology selection and maturation model. The WP4 will provide a compendium of good practices in technology transfer and technology maturation models across Europe and a user guide for their mutual implementation throughout European Regions. The WP4 will enable any bio region partner to propose one development of new drug or a new device and benefit from all the expertise available within the consortium and create, among partners, a virtual incubating system which will enable any start-up company to beneficiate from all the skills present in the network.
- WP5 - Development of sharing network Facilities: many Bio-Regions are attempting to build attractiveness and excellence through heavy investments in research infrastructures whether in technical facilities or in human resources. The role of facilities is crucial: here a large part of the technical experimentation of the maturation process is done but sometimes such investments may appear as little justified, especially if seen from a trans-regional (or wider) point of view.
- WP6 lead by CEBR, is devoted to dissemination of the results issued from WP3-5. WP6 with the help of the Coordinator and the Project Manager will sustain the efforts of the bio cluster partners to ensure the most efficient way of dissemination.



The Bio-CT overall scheme, showing the relationships among the activities: WP5 is circled in red

1.2 WP5 scope: Development of sharing Facilities and deliverables

Through the development and testing of a model to share first phase clinical facilities, a JAP and dedicated guidelines to identify and share key facilities among different clusters will be produced. This will be reached through:

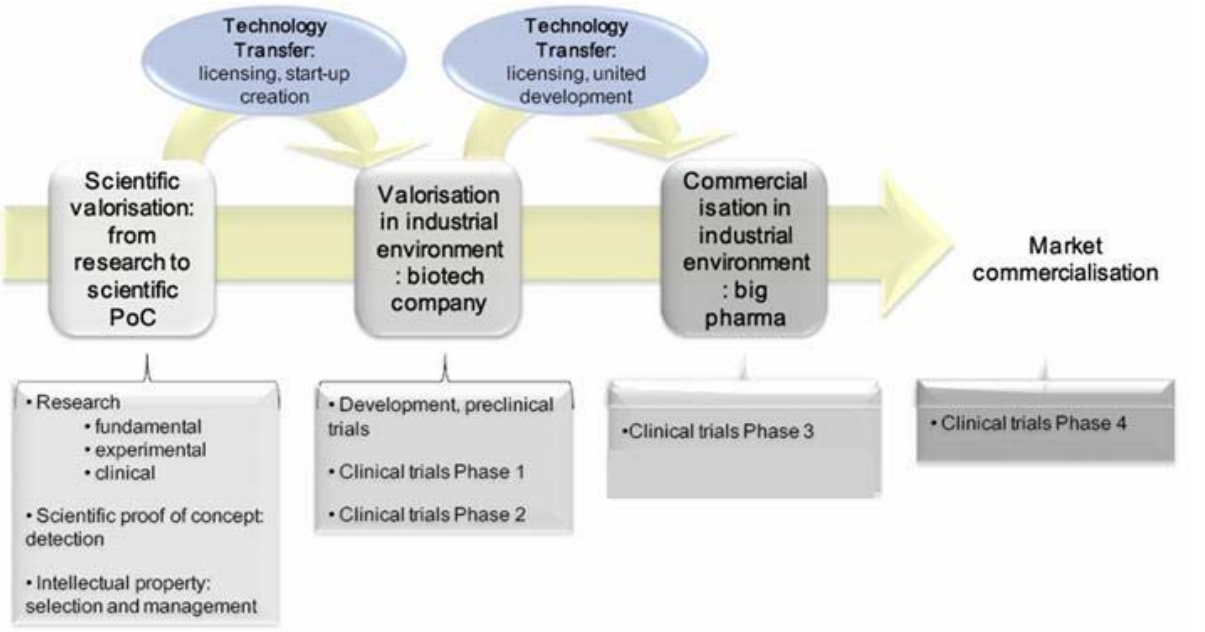
- Selection through a review of critical facilities needed, at regional level, then at consortium level, for upgrading cluster activities from preclinical to clinical phase 1 and likely to be shared.
- Definition of an implementation model of sharing facilities potentially applicable to any biotech cluster that aims to take the step from preclinical to clinical activity.
- Production of a Joint Action Plan chapter on how to share key facilities among different biotech clusters comprising: governance and financing schemes together with a contract model organising access of non local operators.

Expected WP5 results:

- The bio cluster's needs for bio facilities – Experience of some European Clusters: overview of the clusters experience regarding the transition from preclinical to phase in terms of facilities need assessment.
- General guidelines for bioclusters development: report on clusters needs and selection of possible shared facilities. The report will integrate all outcomes of the activities performed in task 5.2 with the goal to summarize and integrate needs of different clusters in a common conceptual framework.
- JAP module on a common initiative to build & share a key facility in a trans-cluster environment. Results of the activity will be the development of the common model for management and use of a trans-cluster shared facility. The JAP module will analyse the different aspects (technical, legal, economic, etc) that will affect the life of the shared facility in order to develop both a proposal to be implemented and guidelines useful to help the implementation of similar actions in other regions. This report will include sections dedicated to governance and financing schemes together with a contract model (business model proposal) organising access of non local operators.

2 The development of a new drug

2.1 The Life Sciences value chain



As shown in the scheme here above, there is a value chain between the scientific research and discovery and the market commercialization. Technology transfer can happen either between the scientific valorization with a proof of concept and the implementation in industrial environment mainly, through start-ups and biotech companies, or between the achievement of the clinical trials phase 2 and the industrial proof of concept and the clinical trials phase 3, especially through big pharma.

The biotechnology value chain involves a series of transformations from discovery of drug or process to final distribution to patients through healthcare facilities.

Primary Activities

Inbound logistics: The goods are highly specialized products, such as stem cells, which have to be incubated at a certain temperature. These are bound to perish soon. Some other

examples of goods required for clinical testing are serum, bacteria, antibiotic sensitivity plates, and culture plates.

Operations: Operations is the most important part of the value chain. It is divided into three sections for the biotechnology industry:

Discovery: The process or drug to be tested has to be invented. A large amount of capital is required to conduct a process or invent a drug. Therefore, intensive research is done before implementation. In a recent research, Tufts estimated that the annual rate of growth in capitalized costs for drug target discovery and preclinical studies was approximately 7.4 percent.

Clinical Test and Legal Issues: The drug then undergoes clinical testing before it enters the market. The clinical testing usually consists of three phases:

1. Phase I: Product is tested on a small healthy control group
2. Phase II: Product is administered to a small group of ailing patients
3. Phase III: Product is administered to a large group of patients to verify the safety, effectiveness, and optimum dosage regimens of the drug

After the drug has passed through the clinical trial stages, it is reviewed by the FDA, which makes the final decision regarding the approval.

Patenting and Manufacturing: Patents are among the most important benchmarks of progress in developing biotechnological products. In the biotechnology industry, patents are critical to raising the capital for research and development. Most biotech companies are novices in manufacturing and face many challenges in the design and implementation of a manufacturing process. In addition to the above, the manufacturing process requires state-of-the-art facilities and has to undergo stringent FDA inspection. These strict conditions of manufacturing require biotech companies to perform manufacturing development and clinical development in tandem for successful product development.

Outbound Logistics: It involves transport of the finished products from research facilities to the hospitals, pharmacies, and clinics.

Marketing and sales: For biotechnology products, marketing and sales is done mostly through trade shows. Television advertisements, journal advertisements, company magazine advertisements, as well as Biotechnology Industry Organization (BIO) can be used to promote a product.

Service: Some companies have excellent customer service and provide personalized customer care and vital information, such as the effects of the drug and the risks involved and increase public awareness.

2.2 Bio-CT selected facilities

BIO-CT main focuses is on sharing platforms / facilities that are accessible and which offer a service-like type of relation and not are research collaboration.

The SWOT analysis, that has been carried out within WP2, served as a background to support the selection of tools, and shown that each cluster is working on its strategic positioning and that everyone is looking for something different from the others.

The SWOT analysis has showed what is strong and what is weak in each cluster, but also the existing tools that they have developed and the tools/needs that remain to be set up or covered.

Each cluster of the BIOCT consortium represents a significant part of the Bio-health potential in its respective country and, for 3 of them (Barcelona, Paris and Berlin), they can be ranked in the top 5 European BIO clusters. Therefore those can provide the BIOCT project with much experience and many assets. Moreover Turin which is not far from the three ones mentioned here above and Debrecen, that is under development and smaller than the

others, can provide some specialties that are less developed in the others or are complementary to the existing potential. For instance, Debrecen can provide a significant potential in clinical trials and testing and certification while Turin can bring imaging competencies and the link between the mechanical field and its technologies and the medical devices.

Therefore BIOCT can build on a solid basis and, by a collective and shared action plan, can reinforce each cluster and its complementarities with the other without avoiding the necessary competition that has to remain among them.

The cooperation among the members of Bio-CT will be facilitated by the fact that the strategic positioning of each cluster that has been put in evidence by the SWOT analysis is in many parts complementary to other positioning. As for example, Paris region needs a stronger biotechnology sector and therefore to increase the number of companies but also their size. The project maturation phase is well developed with plenty of actors (TTO in the research institutes and universities, incubators, seed capital, strong expertise in analysing the projects). However some problems remain in the coordination of the actors, in finding the appropriate human resources, in solving IP issues and in increasing links with the market, in fine chemistry or in animal testing. These two competencies can be found respectively in Barcelona or in Debrecen. Therefore, in this case, BIOCT actors might gather their respective efforts to develop in common a strategy to get the Paris region expertise in project maturation but also to speed up the development of their own Biotech companies. It will be an asset for their big players but also an attractiveness for skilled persons out of Europe that are thinking about coming back.

As for another example, Barcelona can offer good expertise in chemistry and structural biology which is a weakness in Germany and France for instance while Turin can provide expertise in imaging.

Therefore, the SWOT analysis has shown that each cluster is working on its strategic positioning and that everyone is looking for something different from the others. Bio-CT project, by the choice of the tools on which it will focus the next steps of its work and by the way it will implement the cooperation, can help each cluster to reach its strategic

positioning. For instance, clinical trials are a strong issue and, if a shared facility to analyze the results, to set-up a common language, has to be developed, it can be located in a cluster in which this specialty is the most developed.

Moving SWOT analysis out of the 'analysis paralysis' trap and onwards into appropriate tools – adding the valuable contributions that came from the BioCT workshop held in Torino on February 2010 - we have selected criteria that has been used to select specific facilities from each of the three clusters, starting from the information available for each specific facilities such as:

- their **Consistency** with Maturation process;
- their **Excellence** (Qualified, Labeled etc);
- their **Accessibility**: it means the structure/platform is not dedicated to a specific (restricted) group of users;
- their **Lacking** in one of the other cluster;
- if they **Meet Needs** of Projects/Companies in the death valley:
- their **Positioning** along the value chain of the biotech industry (specifically from discovery to early clinical development).

Within the project we have identified and selected a few facilities in order to have **seamless cover from discovery to pre-clinical phase**, being the last one the first crucial point related to the proof of concept and the first technology transfer towards biotech/start-up companies. In other words we selected facilities that are complementary, taking in account the “ideal” flow of activities in drug /product development in the so called “death valley”, trying also to ensure presence and involvement of all the partner regions in the final selection.

As a result of the SWOT analysis and in order to reinforce each cluster and its complementarities with the others, we have identified appropriate facilities available in the

partnering Bio-Regions and likely to be shared in support to the maturation of innovative biotechnology projects:

A. CNG-The Centre National de Génotypage – Paris (FR)

The objectives of the CNG are to develop and apply genotyping and related genomic technologies for the identification of genes associated with genetic or multifactorial diseases. CNG offers state of the art technology to perform scientific or clinical large scale projects aimed at localizing and identifying genes involved in diseases, at discovering polymorphisms or at performing high-throughput SNP genotyping. Internal and collaborative programmes also include those on hypertension, diabetes and HLA compatibility in bone marrow transplantation.

In October 1998, the CNG took over the genomic activities of Généthon, which pioneered genetic studies with the support of the French Muscular Dystrophy Association. .

Many state-of-art resources for genotyping, genetics and high-throughput genetic analysis are available at the CNG. These include DNA banks, techniques for identification and characterization of gene variants, markers and genetic maps, genotyping platforms for microsatellite and bi-allelic markers, physical mapping and positional cloning resources, statistical analysis, genetic epidemiology, HT-sequencing, HT-genotyping, SNP analysis, linkage analysis and bioinformatics.

Services are related to sequencing, genotyping and genetic analysis with the following key characteristics: high throughput (or ultra-high throughput), large/very large scale, on specific genetic loci or on the entire genome, for a number of diverse (human, animal, plant, microorganisms) species: DNA banking ; identification and characterization of gene variants, markers and genetic maps ; genotyping of microsatellite markers ; genotyping of bi-allelic markers ; physical mapping (chromosomes, entire genome) ; positional cloning ; statistical analysis of genetic data ; genetic epidemiology ; HT-sequencing ; HT-genotyping ; SNP analysis ; linkage analysis.

Traceability and Quality Assurance on Data and on Procedures is assured.

B. LIMA – Laboratorio Integrato di Metodologie Avanzate – Piemonte (IT)

LIMA, as building bridge through private and public sector collaboration, incubates both basic and applied Research and Development projects. University and Industry expertise and instrumentation in Cell and Molecular Biology, Mass Spectrometry, Proteomics and Bioanalytics and Pharmacokinetics are available to support integrated activities. University research projects are carried out in parallel with industrial applied research projects and technology transfers. Available also NMR, Bioinformatics and Imaging. LIMA operates from 1999 and has strong expertise on management and carrying out multidisciplinary projects from basic to applied Biotechnology (from Pharma to Agricultural, Food and Diagnostic).
Instrumentation includes 1 Light Cycler, 3 Termal Cyclers, 3 Supercentrifuges, 2 Ultracentrifuges, 3 Spectrophotometers, FPLC and HPLC systems, 2 10L Fermentators, 1 Circular Dicroism System, 5 laminar flow hood, 3 Cell Incubators, 1 Cryostat, 7 Microscopes (1 Confocal, 3 Optical, 2 Fluorescence and 1 Stereomicroscope) 2 Microplate readers, 2 IEF and 6 electrophoresis apparatus, 1 Staining system, 1 Image Scanner, 1CCD camera, Ultraflex II MALDI-TOF-TOF, HCT Plus HPLC/nanoLC-ESI/nanospray-ion trap,
2 LC-MS/MS systems.

The services offered are: Molecular Biology: RT-PCR, sequencing, recombinant protein production and purification, immunological assay, protein interaction analysis. Cell Biology: cell banking, set up of cell models, gene silencing, cell based bio-assays, Immunohistochemistry. Proteomics: cellular proteomics, protein pattern in biological matrices, phosphoproteomics, glycoproteomics. Mass Spectromety: MALDI imaging as a support to biomarkers discovery and protein profiling, and of small molecules (including drug metabolites), protein identification, differential protein expression quantification (iTRAQ technology), purity check of small molecules and proteins. Bioanalytics and Pharmacokinetics: method setup , validation and quantitive analysis of small molecules and proteins (including NBEs and Biomarkers), pharmacokinetics in rodents and PK/PD analysis.
LIMA operates according to a Quality Management System (QMS) inspired to general principles of GLP.

C. FMP Screening Unit – Berlin (DE)

FMP offers researchers from academia and SMEs access to resources for the identification and development of bioactive compounds. Resources comprise a ChemBioNet screening collection (20.000 compounds) and FMP collections with a total number of about 50.000 compounds managed in a Remp store. State of the art detection systems and automation for HTS are established. The major goal is to identify small-molecule modulators for individual functions of proteins. As tools for academic research, these will enable a deeper exploitation of the wealth of genomic information.

Since 2004 the facility supports with know-how and expertise in

- instrumentation for high-throughput as well as high content screening with automated microscopes and cell sorters, capillary electrophoresis, microarray technology, AlphaScreen technology,
- a chemically diverse collection of screening compounds (currently approx. 50,000 small molecules including unique natural products),
- chemistry resources for hit optimisation, quality control of hits and collections
- animal facilities for early in vivo validation,
- bio- and cheminformatics support (SAR, IP searches),
- a comprehensive Chemical Biology database (screening results, assay protocols, and chemical information), and automated data documentation and analysis on the fly.

Services offered are:

Assay miniaturisation for HTS in 384well format and process automation

Automated data analysis, a panel of detection technologies for primary and secondary assays, automated data analysis and reporting (hit identification, data quality validation)

Other services

- Project management support
- Standard contracts available

- "After sale" support

Interested users have to submit a short project application form with descriptions of the test system plus controls and a detailed workflow of the assay including data already measured in larger scale set up. An account for the Chemical Biology database is provided. Users will send scientists and reagents for assay transfer and assay optimisation to the platform. The staff of the platform sets up automation for HTS, automated data analysis for hit identification and hit clustering as well as control of process stability. Up to 352 hits may be picked for validation of compound activity through IC50 determination. For selected projects, users can ask for advanced modelling and chemistry support in order to optimize hits. Users are advised to inform their local technology transfer agencies about results to enable effective commercialization, i.e. in partnership with industry.

D. High-Throughput Screening (HTS) facility – Debrecen (HU)

The HTS facility offers contract research including assay development, and screening of compound libraries for investigators of the University of Debrecen as well as for external partners.

The HTS facility is equipped with: Tecan Freedom EVO 150 liquid handling robot with 8 channel pipetting head (disposable or fix tips, low volume option); 96 channel head; independent robotic arm; pin tool (for compound transfer in nanoliter quantities); shaker module (2 microplates); incubator module (6 microplates). Plate washer TECAN Power Washer 384 accepts 384 well plates (96 well head to be purchased soon). Victor3 V multimode reader with 2 injectors, absorbance, fluorescence intensity, fluorescent polarization, time-resolved fluorescence, luminescence, 1-1534 well plates, top and bottom reading, incubation. Cell culture unit (laminar air flow box, CO2 incubator, inverted microscope)

The HTS facility offers contract research including assay development, and screening of compound libraries for investigators of the University of Debrecen as well as for external

partners. Biochemical and cell-based assays for the identification of compounds with antioxidant, cytotoxic, cytoprotective, enzyme inhibitory, activity.

E. Research Applied on Laboratory Animals (PRAAL) – Barcelona (ES)

Research involving laboratory animals is centralized in the Animal Research Centre (SEA), which is located in the Modular Building of the Parc Científic de Barcelona (PCB). Its services are available to users of the PCB and the Universitat de Barcelona (UB), as well as to researchers from the private sector and other public institutions.

Occupying 920 m2, the installations of the SEA-PCB have been designed to house rodents and aquatic species. They include an Experimental Unit, equipped with all-round laboratories for the collection and preparation of samples and a Specific Pathogen Free (SPF) facility which includes, among other facilities, a Transgenic Unit in which genetically modified organisms (GMOs) are produced and kept.

- To provide for the care and welfare of laboratory animals, and to carry out periodic health monitoring.
- To cover the users' needs by providing them with the assessment and equipment necessary to carry out their research on laboratory animals.
- To ensure observance of all legal and ethical standards concerning to the use of animals for research and other scientific ends.
- The SEA-PCB houses small rodents. However, the multifunctional design of the animal rooms also allows less used species to be housed, such as rabbits, guinea pigs and amphibians.

Services included in the charges are:

1. Animal Housing

- Purchase management: Import/Export
- Quarantine and health control

- Maintenance: cage changes, diet, drink, cage labeling
- Sterilization of material for the SPF zone: bedding, cages, feed
- Veterinary care and assessment in animal welfare

2. Maintenance and operations of the installation:

- Computerized control of environmental conditions, which incorporates an alarm system
- 24 h Maintenance service
- Control of environment and water contamination
- Log of equipment maintenance
- Computerized management programme
- Compliance with SOP
- Waste management

3. Users:

- Provision of clothing
- Support services:
- Veterinary care and animal welfare
- Updating regulations related to animal research
- Notification of specialized courses
- Organization of periodic seminars
- Use of shared laboratories and equipment
- Services related to the Animal Welfare Committee:
- Assistance with the writing of experimental procedures
- Evaluation of Procedures
- Report writing
- Formalities of user accreditation
- Logs of procedures, reports, acts and list of accredited personnel

4. Services not included in the charges Specific techniques:

- Kinetic studies and toxicity testing of new drugs
- Surgical procedures
- Necropsy and tissue sampling
- Mating, control of vaginal plugs, weaning and separation by sex
- Decontamination of pathogenic microorganisms by means of embryo transfer

5. Production of genetically modified organisms (GMOs).

6. Production of transgenic and knock-out animals (including KO, Cre/lox P):

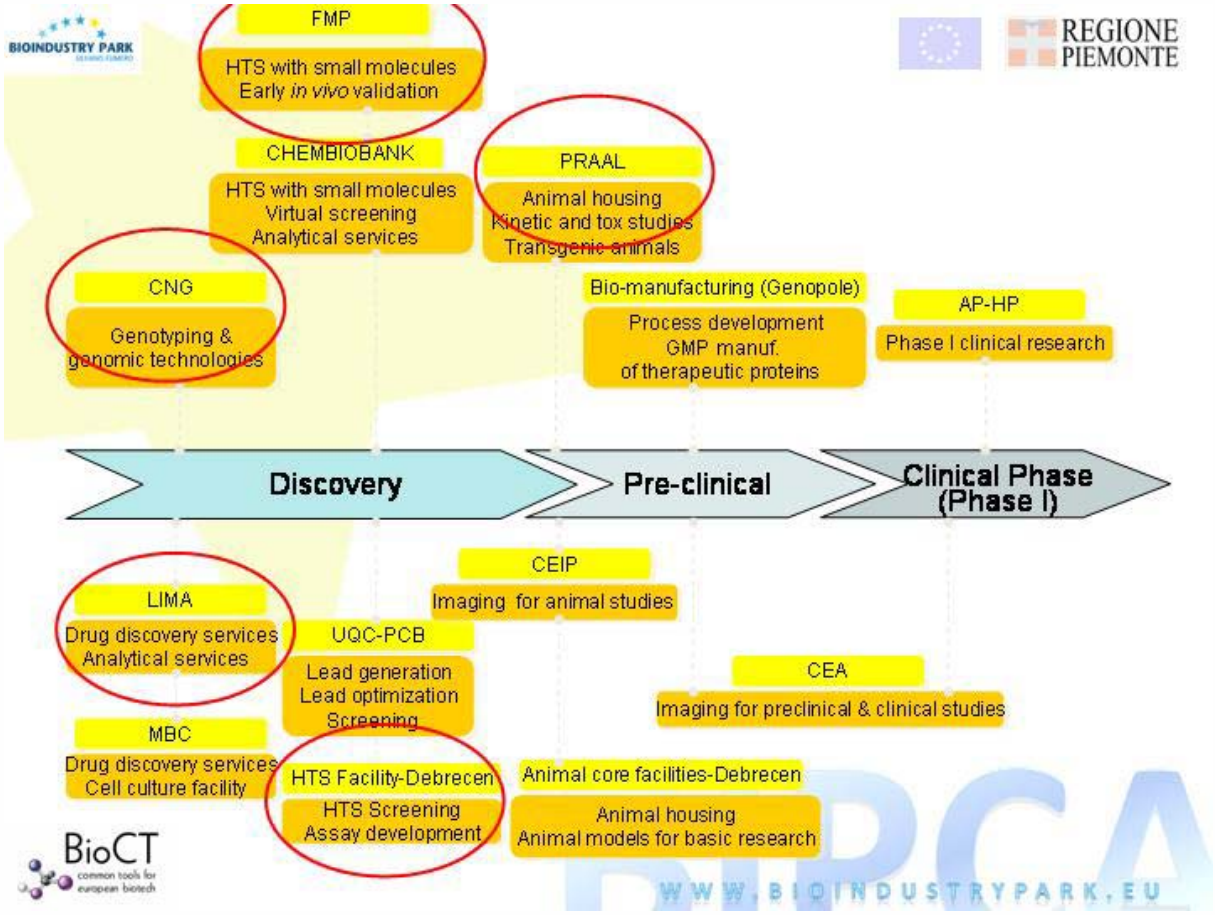
- DNA microinjection
- ES cell microinjection
- Complete phenotyping of GMOs :
  - Analysis of blood and biochemical parameters
  - Anatomopathological studies
  - Behaviour trials
  - Neurodevelopment testing

To ensure optimal operation, the SEA-PCB has established a set of regulations which define its activities, managerial structure and financing. Furthermore, this centre has drawn up an Animal Care Manual which sets forth the rights and duties of its users and staff and also offers recommendations on animal use. This document establishes Standard Operation Procedures (SOP) and Good Laboratory Practices (GLP).

Conclusions

Each facility selected within the BIOCT consortium represents a specific part of the Biotech industry value-chain. HTS-Debrecen and FMP are in the very upper end of the chain and can be used for the identification of small molecules as chemical, diagnostic and therapeutic

tools and for the identification of biological macromolecules as drug targets. CNG can develop and apply genotyping and related genomic technologies for the identification of genes associated with genetic or multifactorial diseases thus representing a valuable discovery tool for the identification of gene variants, markers and possibly new targets. LIMA offers comprehensive services in support of biomarker/drug discovery and early preclinical development studies and many of the services and technological platforms can be complemented by the broader range of animals, including transgenic and knock-out animals, provided by PRAAL..



Advantages for the facilities of being involved in such initiative are numerous:

- A bigger "market" for services: usually facilities are conceived to offer service to a local market or even to a very limited "captive" market. The only exceptions are those facilities that, from the very beginning of their life are conceived to be "international". In any case, also for those facilities, a better "marketing proposal" could be a plus.
- Better synergies with other complementary facilities, so they could be able to follow the development of a product through many different steps and to work with complementary actors
- Standardization of internal document and a boost to quality level assurance: facilities with more difficulties in contact with the market could learn from more advanced facilities
- Better understanding of market needs: the BioCT activities and tools will help them to move from fundamental research facilities to more market oriented services platforms
- Better technological integration between facilities: solutions are more and more the results of different technologies/services linked to each other. And of course integrated alongside the product value chain.
- Possibility to leverage their internal asset through a pan-European offer. This will also provide more visibility out of the local territory (and, why not, ALSO ON the local stage).
- If they are integrated in an international system of services, more visibility means more clients, more clients mean more money, more money and means more resources to invest in R&D and new technologies.

All these aspects were shared during the exchanges that the partners had alongside the development of the project and in particular during the BioCT workshop in Torino, where is had been clearly stated that the facilities that were going to be selected had to be provider of services and not of general capabilities. From a market point of view the capability to offer a broader spectrum of services to local clients (within a reciprocity approach) with other facilities in other territories is a plus for the competitiveness.

This point is also important moving towards the JAP. The JAP will have to take into account two different aspects: one is public and is related to policies. But the other one is linked to the commitment of the different actors: the role of the JAP will be that of determining which degree of commitment the facilities have to take versus the public policies.

Different solutions could be envisaged, ranging from a simple list of services that a client can "pick-up" (an approach similar to the Swedish Tools of Science) to unique offer with a single pan-European entry point. Role of the partners will be that of exploring the different possibilities and to find a shared solution able to satisfy everybody.

3. Sharing Services and facilities (or Outsourcing Research Facilities)

3.1 Market opportunities for Shared Services Approach

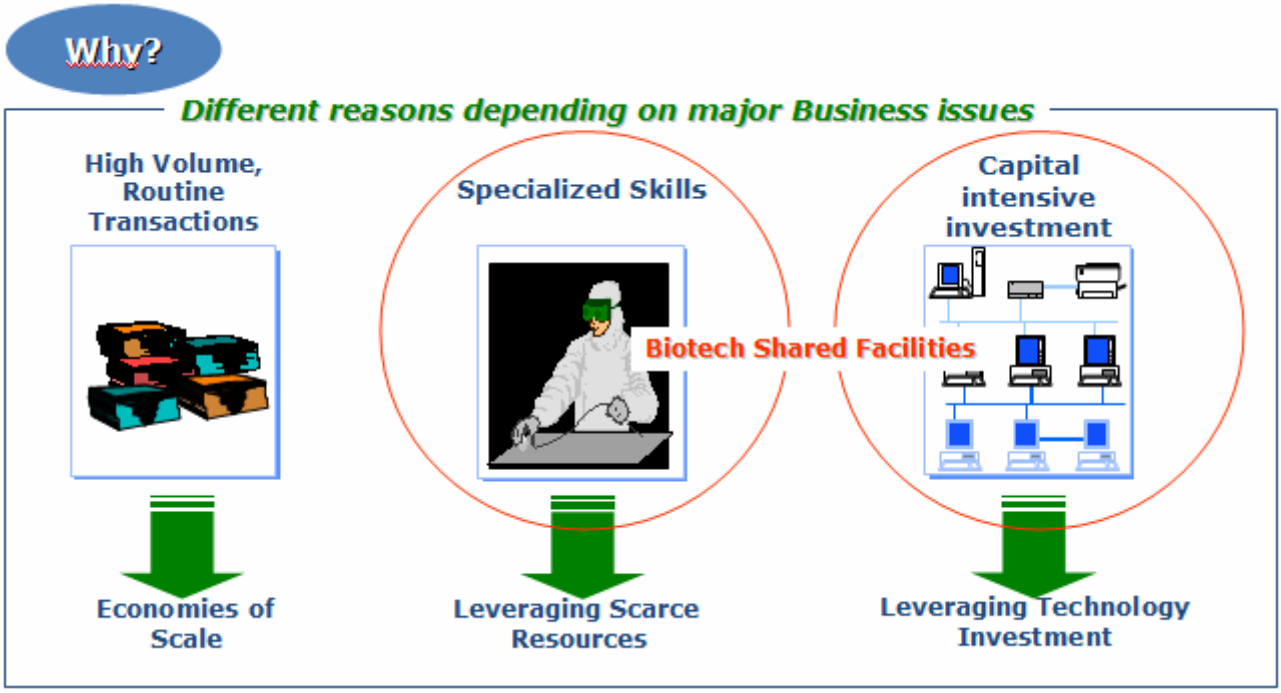
The Objective of the Shared Services – or Shared Facilities or Outsourcing Research Facilities - is generally to consolidate and redesign staff and support functions to deliver the most cost-effective and highest-quality services possible.

Shared services are frequently mentioned as a way of reducing costs, such savings are likely to come from:

- Staff rationalisation through economies of scale
- Adoption of best practice in working practices across the partnering organisations. This should lead to reduced duplication and mean more
- customers are dealt with at the first point of contact
- Lower accommodation costs by moving to a single site
- Fewer management overheads and more streamlined reporting procedures
- Cheaper procurement through aggregated demand.

However, 'efficiency' should be interpreted in a wide sense, since experience has shown that shared services deliver better Corporate or Cluster performance (non-cashable gains) as well as financial savings (cashable efficiencies). Indeed, if organisations focus solely on cost savings, they are likely to miss the

chance to improve service outputs by establishing better processes, producing quality management information and introducing greater professionalism and career opportunities.



Academic science commercialization through University spin-offs or patents has been growing since the mid 90s. The first biotech firms started up within academia to be able to use unique research facilities with the complementary competences. Since the development of genomics and tools for 'mass gene and protein exploration', instrumentation has become more and more resource-consuming, making sharing research facilities a growing issue.

The biotech industry to date has been largely built with a combination of tapered and quasi integrated strategies. Even the industry's largest and most successful players are not fully integrated organizations. For example, Genentech relies upon marketing and distribution arrangements with other biotech and pharmaceutical companies, and Amgen has similar marketing and distribution arrangements as well as contract manufacturers for some of its products. Almost every biotech company has one or more research relationships with academic institutions and/or contract research organizations (CROs).

These strategies have been employed for decades in large part because of the enormous costs of building vertically integrated resources in relation to research, clinical trials,

manufacture, distribution and sales of drugs. The pharmaceutical industry has already made the capital investment into exactly these types of resources and has a constant need for new and innovative drugs.

In the case of a biotech company, Sharing Facilities (or outsourcing research facilities management) may essentially mean that the biotech company's integrated resources are limited to a key management team and the facilities needed to support their activities. The virtual organization strategy appears to be well suited in the biotech business because of the critical and otherwise conflicting needs for flexible access to the best worldwide thinking and resources, conservation of capital and speed in business decisions, processes and market entrance.

3.2 Organizational Strategies: "Virtual Company" concept

Scientists are constantly furthering knowledge and understanding of genetics and exploring how to solve complex problems by changing the basic building blocks and structures of life. The purpose of this section is to question whether the same sense of exploration and disruptive thinking should be applied to the basic business models that are used to build biotech companies and whether one particular organizational theory, the "virtual company," presents a theory that is particularly well suited to the development of fast growth, biotech enterprises.

Four main organization categories, ca be briefly summarised:

- **Full Vertical Integration**: Organization seeks to control the value chain through direct corporate ownership of business units at each stage of the value chain.
- **Tapered Integration**: Organization has direct corporate ownership of many of the business units in the value chain, but outsources one or more stages of the value chain. The degree of vertical integration will be different from organization to organization.

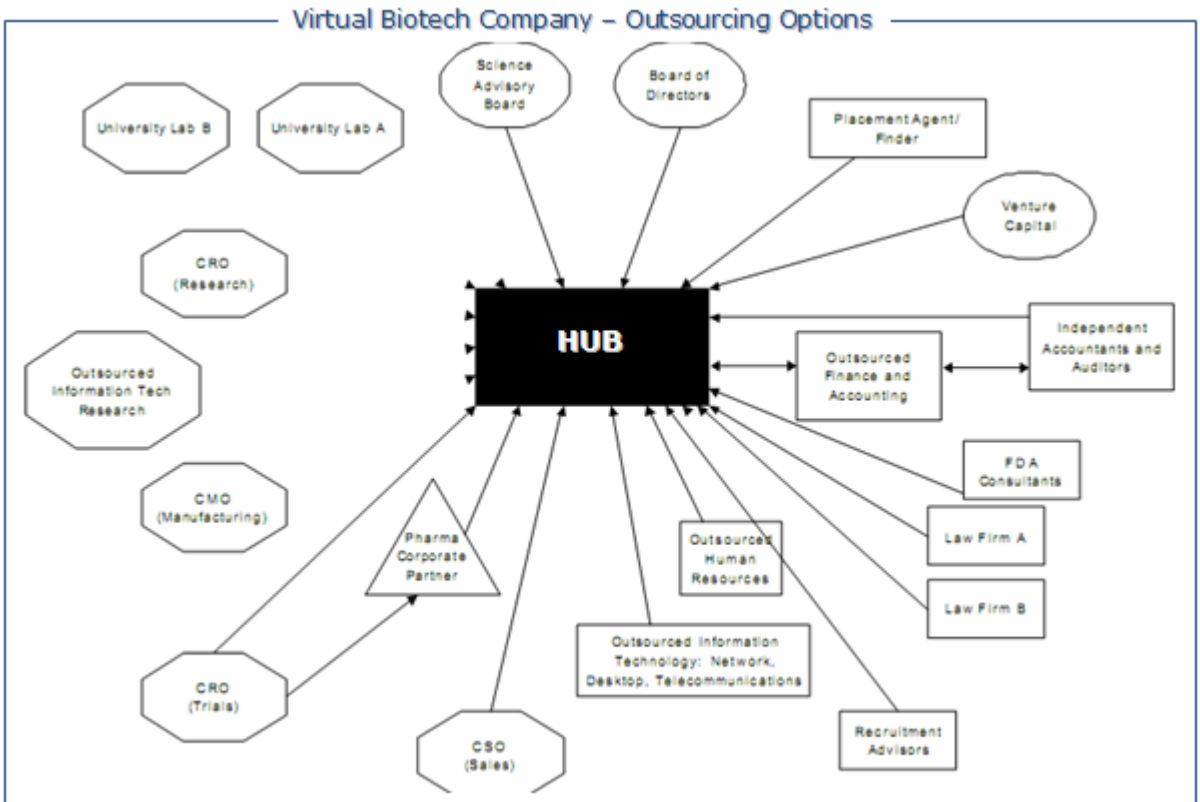
- **Quasi-Integrated**: Organization seeks to control value chain activities through joint ventures with other firms and organizations. The degree of vertical integration will be different from organization to organization.
- **"Virtual"/Non-integrated**: A collaborative network of independent organizations and people sharing skills, costs and access to one another's markets, linked by information technology. The virtual organization only retains its "core competencies" and maintains control over its value chain through contractual arrangements.

The virtual organization is designed to maximize the organization's ability to meet these needs of flexibility, access to the best resources and speed. Instead of investing heavily and in advance in infrastructure and employees, the virtual biotech company can readily shift from one research program to another and contract for services and knowledge from experts all over the world. Valuable research dollars can go to the researchers that best meet the biotech's development, cost and timing parameters. The global/European market for services creates greater supply and thus better service delivery as a result of greater competition.

3.3 Shared Services Key Success Factors

Most people in the biotech industry will be familiar with some of these forms of outsourcing but may never have used the term outsourcing to describe these relationships. For instance, Sponsored Research Agreements between a biotech company and a university often go hand- in-hand with a license from that university to the biotech company of core technology and intellectual property rights. For purposes of this discussion the Sponsored Research Agreement is being characterized as an "outsourcing" to the university of work that would otherwise have been carried out by the company after establishing the necessary integrated resources (i.e., leasing lab space and hiring researchers).

In current market reality, the biotech company – especially SME – may have a strong interest to enter into the Sponsored Research Agreement, either because the company does not have the capital to build the research facilities or because the inventor/primary investigator is not interested in leaving academic research (or other research context) to join the company . In addition to sponsored research at universities, biotech companies are increasingly outsourcing research services, clinical trials, together with more common operations such as manufacturing, distribution and sales and marketing.



Shared Services organization approach reduces the amount of vertical integration - and invested capital needs in biotech research facilities case - and lead to a level where all that is left is a "hub" consisting of the core competencies of the organization which manages a series of collaborations and contracts with third parties.

According to Nigel-Howard-Mayer-Brown-Rowe-Maw, in order to be effective and work properly, those "virtual organizations" or "Shared Services Networks" need to strongly address at list partner size, organizational, commitment and technology issues, as for example:

- Highly complex R&D and international competition leads to more cooperation, particularly amongst small and medium sized organizations.

- Costs of managing a network of collaborations can be reduced if trust and commitment can be built between the participants.
- Commitment is hard to gain and make proportionate. Commitment is also easy to lose and thus commitment should be given the opportunity to grow in collaborations.
- Participants in any collaborative network have differing interests and differing levels of commitment and motivation. This problem can be addressed in part by open communications between the participants, particularly in terms of the core competencies and specialist talents/resources of each participant, and through an understanding of the difficulties of accomplishing the same goals outside the collaboration. *There needs to be clear communication with organizations that are external to the collaboration, so that the rest of the world understands the benefits and capabilities of the collaboration.*
- Information technology can be key in enabling the communication flow.

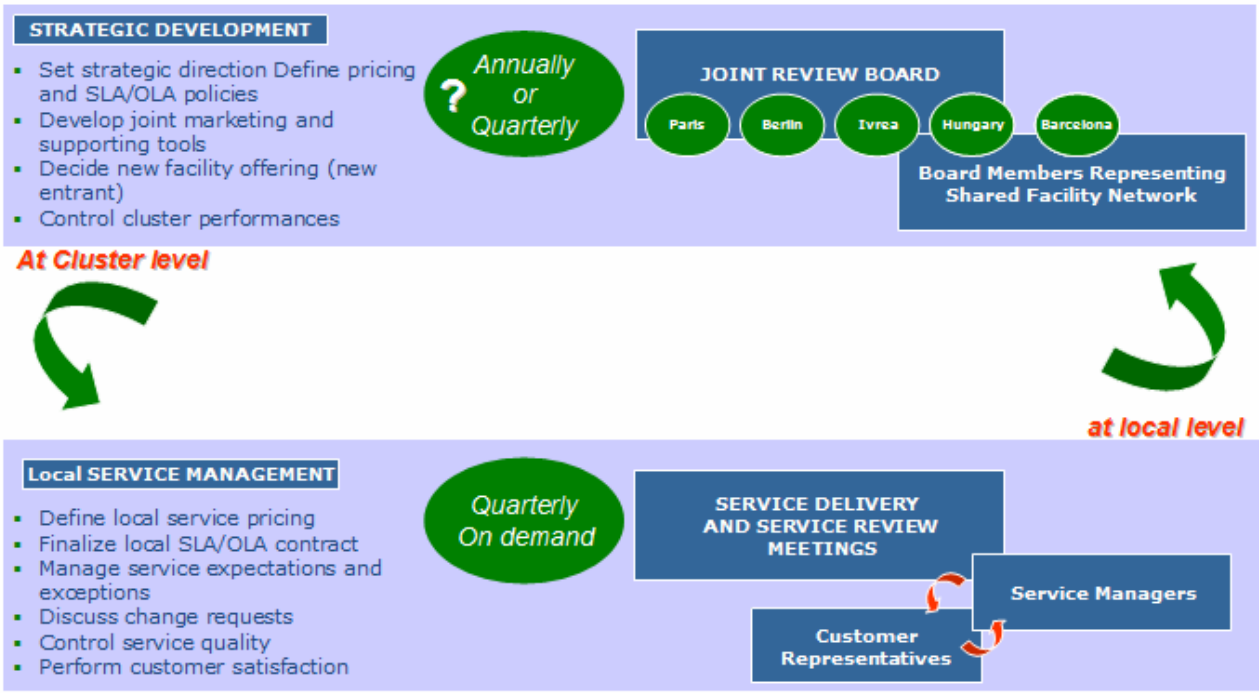
In other words, to move to a fully virtual organization, biotech companies would have to increase the number of their contractual arrangements and seek to have those arrangements work with one another.

One problem is that the suppliers will need to interface with each other and those interactions can lead to confusion, missed responsibilities and disputes. As can be easy to understand, the virtual organization can have a myriad of different relationships and in many cases those relationships and the contracts that govern them need to be coordinated.

Failure to adequately address the needs of other dependent services in the contracts that govern an outsourced service could seriously undermine the benefits of the two sets of arrangements. To some degree outsourcing arrangements are only just starting to tackle this issue. Flexibility, in terms of being able to change or terminate service arrangements, is key to tackling these issues. Adding special contract provisions that require suppliers to cooperate and coordinate with other third party suppliers are also being proposed and negotiated. Probably the most important thing is for the customer to envisage an overall strategy for their outsourcing, so that to the greatest extent possible they can identify areas

of common dependency between suppliers and address those points in the contract established with each supplier.

The picture below aims to suggest a possible virtual relationship model between strategic facility management development (at head of cluster level) and local service management level.



Note:

Here **SLA** is an acronym for Service Level Agreement and **OLA** is an acronym for Operating Level Agreement. Both the concepts are clarified on page 23.

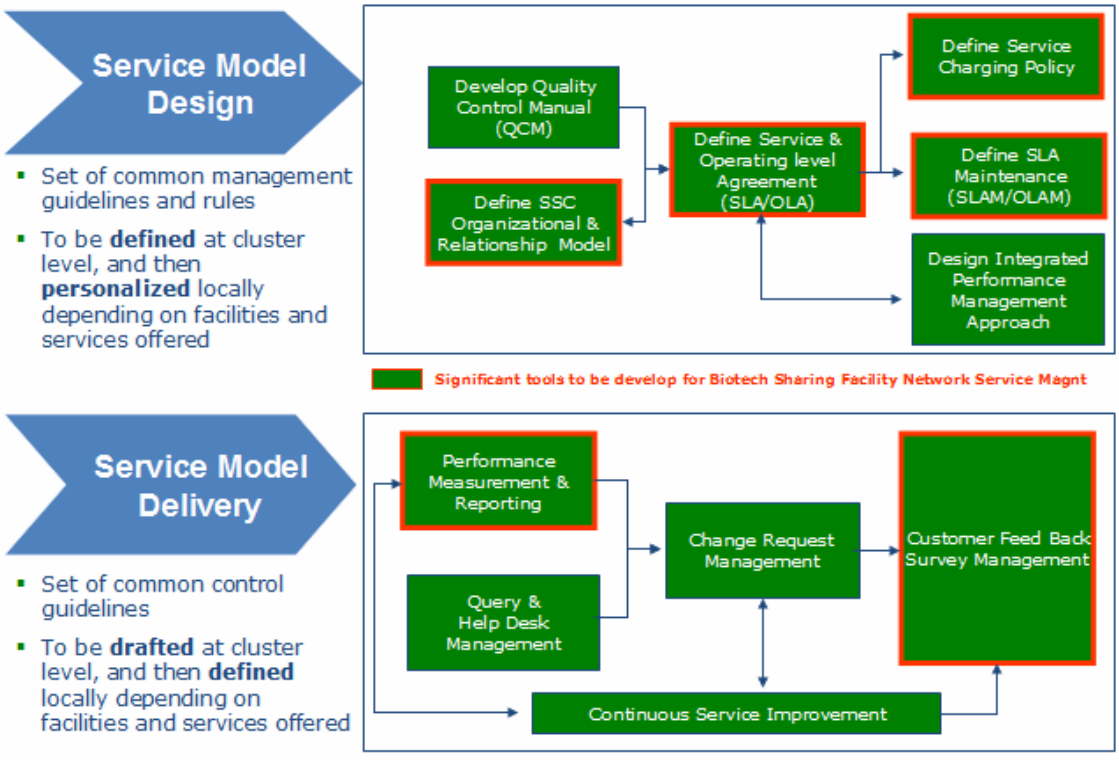
4. Service Governance : contracting, management and control

4.1 The strategic importance of the service model

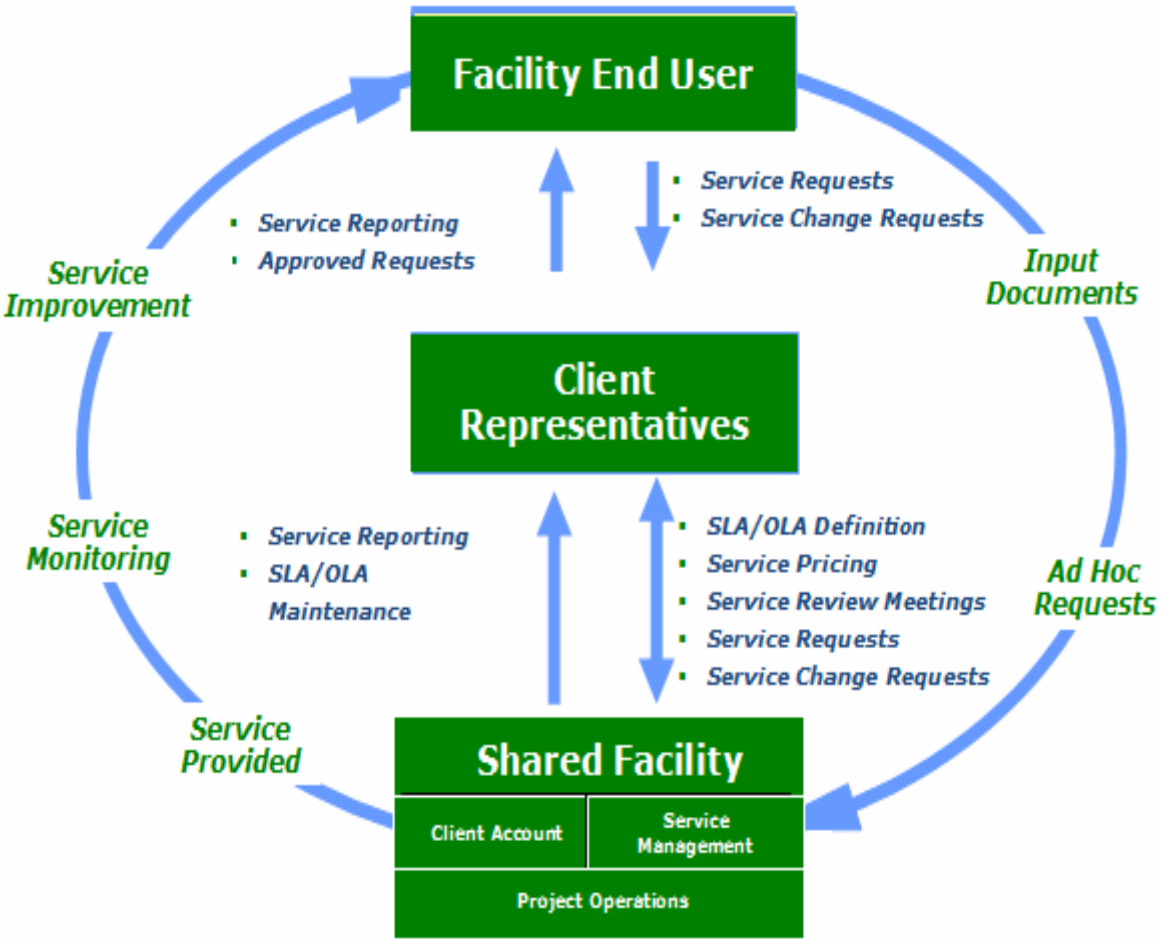
The organizational structures used by biotech companies today are at one step on the evolutionary ladder towards a truly virtual corporation. A virtual organization strategy does appear to present potential efficiencies and advantages for building a biotech company, and with an ever-increasing range and number of suppliers, there are good reasons for giving the strategy renewed consideration. Appropriate planning, structuring of contracts and management of suppliers are all critical to realizing the strategy and making it work.

Experience in dealing with those issues has provided a number of contractual devices and mechanisms that can be employed to the biotech company's advantage.

World-Class Service Governance is the starting point do correctly design and then manage the service: the interactions between the customer and the supplier are impacted by various factors that have to be addressed in the services contract. Following picture summarize the method and related steps to define a Service Governance Model:



The picture below illustrates the potential service interaction model between customer and supplier and related service management and control tools:



4.2 Key issue for service (outsourcing)contracting: General Provisions

According to N. Howard , the interactions between customer and the supplier are impacted by various factors that largely emanate from the outsourced services contract.

The hub's degree of dominance (see picture next page) will be governed by the number of arrows that it has at its disposal and the extent to which it can avoid a contract that gives the supplier its own set of arrows. As the following examples demonstrate, the degree of dominance in a hub/supplier relationship can be materially impacted by the terms of the

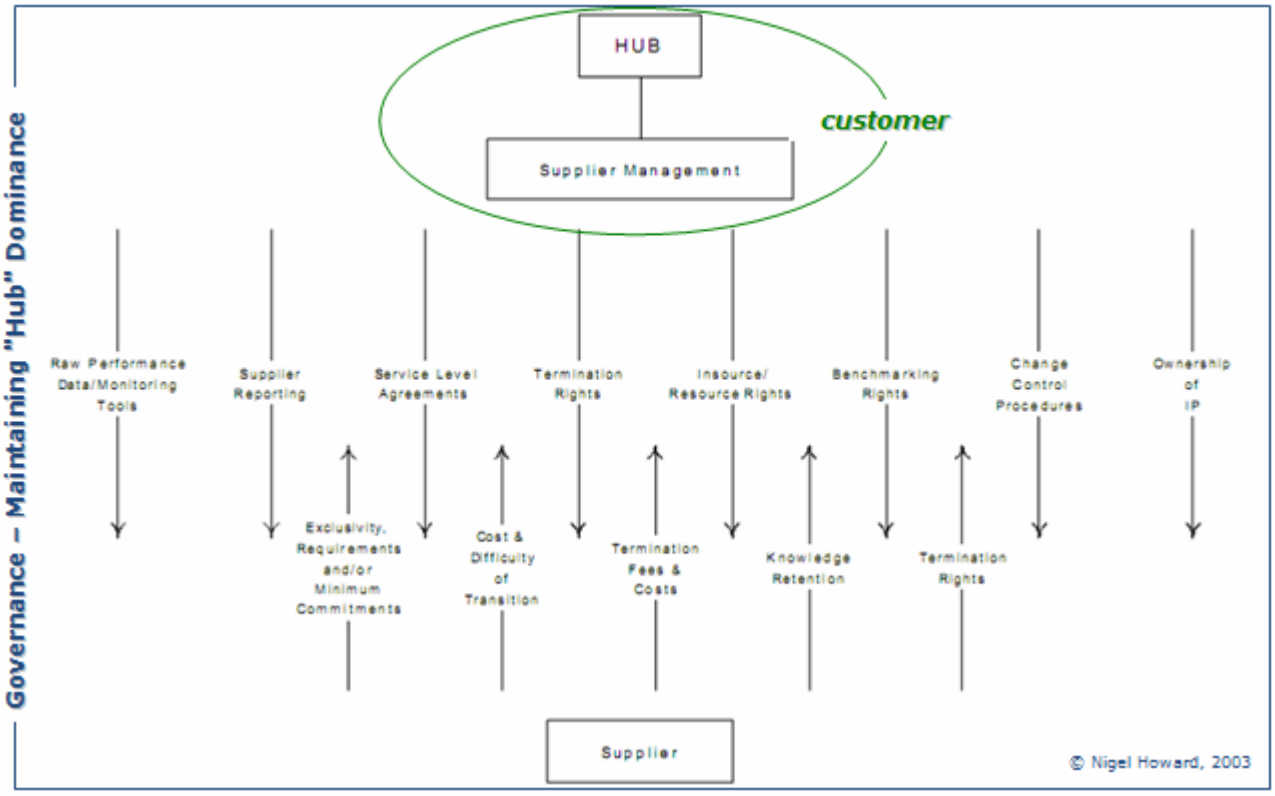
contract. The author also suggests ways in which the "hub" can maximize its dominance through careful negotiation of such provisions and how the maturity of the outsourcing industry has provided tools and practices which facilitate a virtual organization strategy.

Loss of control and management burden are issues that need to be addressed in outsourcing and fall within the broader category of governance of the outsourced arrangement. It is necessary with any outsourcing arrangement that the customer give up some degree of control to the supplier and the need to retain hands-on control can be a significant factor in decisions not to outsource.

Control of the end results often depends on the leverage (also known as dominance) of the customer. Dickerson discusses the importance of "dominance" in the relationship between the customer ("hub") and the suppliers to a virtual organization. It is undoubtedly a key factor in achieving success in any outsourcing arrangement and the following section of this paper discusses some of the main ways in which this can be achieved.

Dominance may be difficult to maintain and the customer may have differing degrees of dominance in particular arrangements, but with careful planning and structuring dominance can be maintained.

Major issue in contracting phase, which is the starting step to organise, manage and maintain the service will be for Biotech industry Dominance governance. Below are summarised some tips, erasing from best practice experiences shown in technical literature.

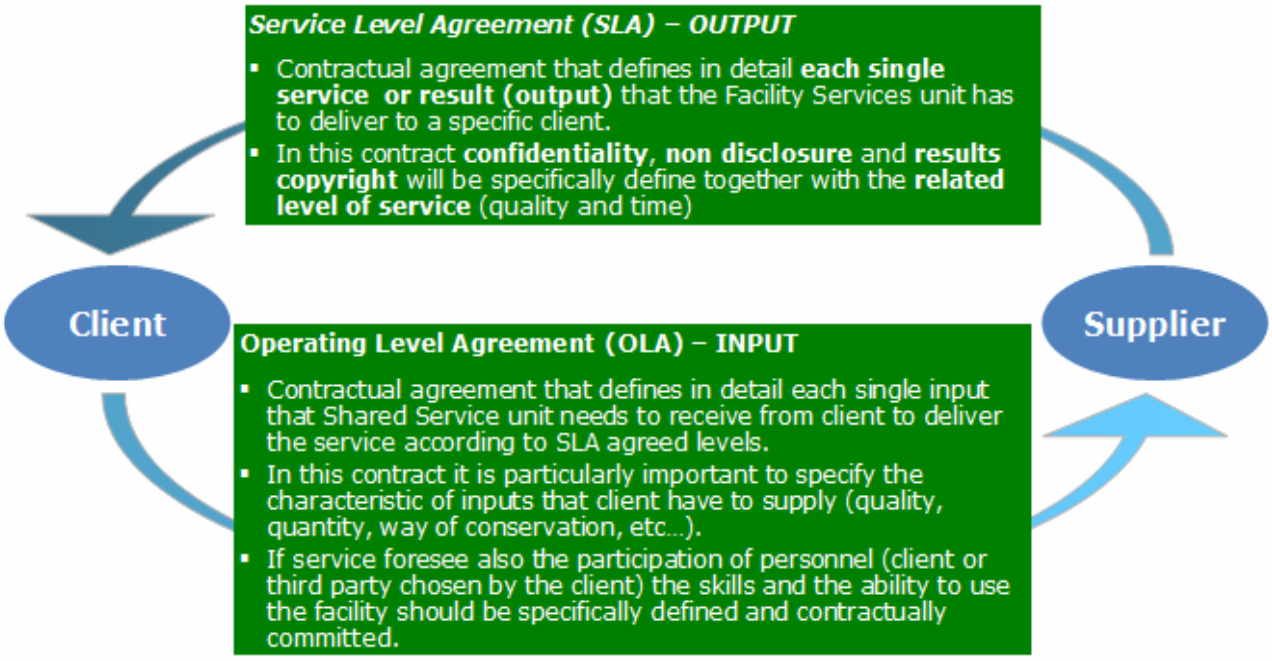


- **Termination Rights.** Prior to engaging outsourced resources the customer has the ultimate leverage and flexibility of choice: if a supplier does not provide what the customer wants the customer can chose the supplier's competitor. Market forces, supply and other factors may limit the decision, but usually the customer is in the driving seat. That degree of dominance in favor of the customer would ideally be preserved during the life of the outsourcing arrangement so that the customer could again chose to move to a supplier's competitor if it was no longer satisfied with the incumbent supplier's services. This degree of flexibility is often not possible. The supplier will usually make an upfront investment in the outsourcing arrangement that it will need to recoup over time. Thus the supplier will demand that the customer provide some degree of long-term commitment to the relationship. In the context of sole sourced information technology outsourcing this has often meant a commitment by the customer of between seven and ten years in length. This issue will need to be analyzed and addressed with each arrangement and a fair balance struck between the considerations of the customer and the supplier.

- **Insource/Resource Rights.** Similar to the right to terminate, the terms "insource" and "resource" refer to rights to recommence performance of the outsourced services with integrated resources ("insourcing") or to contract for a third party to perform the outsourced services instead ("resourcing"). This is often used for more incremental changes to the work given to the supplier. These rights are very useful, in particular because while a supplier may be meeting or exceeding expectations in certain areas of the services, there might be discreet areas where the customer would like to pursue an alternate solution.

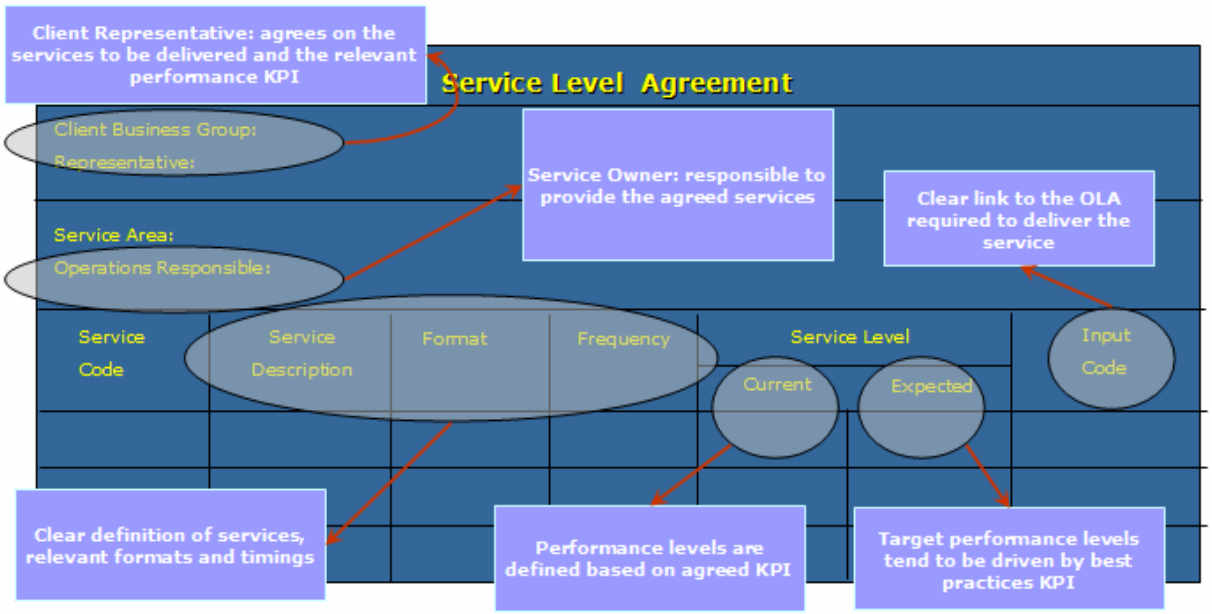
- **Service Level and Operating Level Agreements (SLA/OLA).** Formal agreement signed-off between facility supplier and Client in order to define responsibilities and to motivate both parts to a continuous focus on end-to-end process improvement at the proper negotiated price.

  Every outsourcing agreement should contain service level agreement (SLA) and operating level agreement (OLA) against which the service provider will be measured. If the customer does not have sufficient data upon which to establish service levels, or does not wish to take the time to collect such data, the customer should start by requiring the service levels to be at least as good as what the customer received prior to outsourcing and/or a mechanism should be included in the outsourcing agreement for determining how the service levels are ultimately established. If the service provider fails to meet the mandated service levels, the customer's remedies should include the reduction of the service provider's fees (performance credits), the ability to insource or resource the service(s) at issue, and/or the right to terminate the affected service(s) or terminate the entire outsourcing agreement. For other areas of outsourcing, particularly those where there is less standardization in processes, the establishment of performance levels may be more difficult: t*his is one area where the biotech industry could use more planning because the industry's current outsourcing arrangements tend to have relatively few performance measurement provisions.*



Commonly, each facility to be shared in service will have specific and unique characteristic to be addressed in contracting phase, moreover in Biotech facility management majority of services will be designed and defined, according with client requirement in SLA/OLA formalization and subscription.

Below it is possible to find an example, as reference, of a SLA structure for repetitive services:

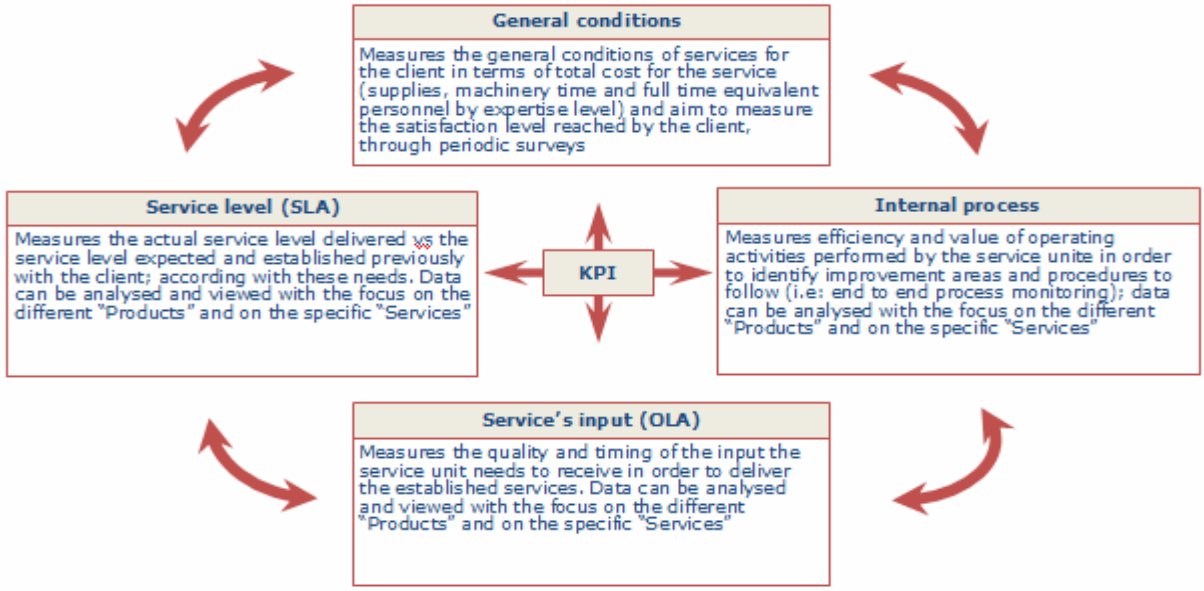


- **Change Control Procedures.** It is inevitable that change will be required in any outsourcing arrangement. Particularly for longer-term arrangements, it is impossible to accurately predict all the needs and requirements of the customer, or how they will change over time or be impacted by changes in the marketplace. Thus a successful outsourcing arrangement needs to include a procedure by which change can be assessed and dealt with. Certain types of changes and variations should be built into the arrangements with preset adjustments to the terms to take care of their impact. For instance, certain changes to volume of services or deadlines for delivery could have a predefined cost impact in terms of adjustments to the prices for the services. Other more fundamental changes to the services require a process for assessment and negotiation of the applicable contract changes. Having these procedures clearly established will enable the customer to maintain some degree of dominance even when change is subject to negotiation, because the customer will at least know what the

change process is and when it has been exhausted. The end of the change control process may trigger rights for the customer to go elsewhere for the changed services.

- **Change control procedures** must be **specific, documented, agreed** in order to avoid long and protracted discussion as to their application
- A **change request program** should be developed containing :
  - Specific description and reason of each change request
  - Impact on service charging, processes, IT and people
  - Authority to proceed with the change request

- **Key Performance Indicators: Data/Monitoring Tools/Supplier Reports.** Balance Scorecard Approach for KPI Reporting to measure internal performances and Input-Output (OLA-SLA) quality and client satisfaction is highly recomended. A customer's ability to manage the supplier is highly dependent on the degree to which the customer has information concerning the supplier's performance. Setting mutually agreed means to measure performance and monitoring results against required levels of performance gives both customer and supplier an objective basis on which to assess the success of the relationship. The supplier should regularly report on its performance and the customer should have access to those reports and the underlying data to make its assessment of that performance.



- **Ownership of Intellectual Property (IP)**. Intellectual property ownership is often one of the most heavily negotiated terms of any outsourcing arrangement. Customers need to determine what ownership regime they wish to establish with their service provider. Some customers demand ownership of all of the intellectual property developed under an outsourcing agreement, regardless of whether the service provider developed the IP alone or together with the customer's employees. On the other hand, service providers often demand ownership rights or at least a license arrangement so that the service provider can use the intellectual property internally or to provide services for other customers. To the extent ownership vests in the service provider, the customer needs to ensure that it receives sufficient rights to use such IP during and after the term of the outsourcing agreement and what restrictions, if any, should be placed on the supplier's use of the IP. To the extent ownership vests in the customer, the customer may have influence over the supplier as a result because if the supplier later needs to use the IP for another purpose it must first ask the customer for a license. The customer might use the supplier's need for additional rights to the IP as leverage to gain some other concession from the supplier. Defining which party owns various types of IP, and how each party and each type of IP may be used, is important for any outsourcing arrangement. Careful

analysis of the core and non-core strategic issues for the customer will help determine what ownership regime is right for the customer. If a customer can obtain ownership of IP, then those ownership rights may give the customer an additional sphere of influence over the supplier.

- **Collaborative Research Agreement.** The objective of writing a collaborative research agreement is to clarify for both parties what they are trying to accomplish together and to clearly set forth the rules that will govern the collaborative effort.

  A good partnership must be mutually beneficial, and an effective collaborative research agreement will help both parties understand and accept mutual benefit as a goal. An effective agreement must be based on an actual win-win relationship, one that is truly mutually beneficial. So to start with, the concept of the collaborative research project must involve a research project through which both parties benefit from the work that will be done. A poorly written agreement can tear apart an otherwise harmonious relationship. On the other hand, a well-written agreement, in which all parties understand their responsibilities, will build and strengthen a productive scientific relationship. An effective agreement will be clear both to the researchers doing the research work and to the managers of both parties. And a well-written collaborative research agreement can lay the groundwork for moving the results of research toward commercialization. Most collaborative research agreements have five general parts. The agreements can be somewhat flexible in the terminology they use. The names assigned to the subparts are not terribly important. What is important is that the agreement covers each the following points:

  - statement of objectives
  - statement of work
  - general provisions
  - budget
  - list of materials

- **Confidentiality/non disclosure agreement.** This is one of the most important parts of the contracting frame in biotech facilities service modelling. A non-disclosure agreement (NDA), also known as a confidentiality agreement, confidential disclosure agreement (CDA), proprietary information agreement (PIA), or secrecy agreement, is a legal contract between at least two parties that outlines confidential material, knowledge, or information that the parties wish to share with one another for certain purposes, but wish to restrict access to by third parties. It is a contract (or a specifica part of it) through which the parties agree not to disclose information covered by the agreement. An NDA creates a confidential relationship between the parties to protect any type of confidential and proprietary information or trade secrets. As such, an NDA protects non-public business information. NDAs can be "mutual", meaning both parties are restricted in their use of the materials provided, or they can restrict the use of material by a single party.

- **Exclusivity/Requirements/Minimums**. Customers should not enter into an exclusive relationship, requirements contract or minimum purchase commitment with a supplier unless faced by some compelling need to use just one specific supplier or the customer receives such huge price concessions that it justifies the loss in flexibility. While certain arrangements may by their very nature necessitate that the customer commit to purchase a certain minimum volume from a supplier, a customer should always maintain the flexibility to buy services elsewhere if at all possible (see discussion above).

- **Termination Fees and Costs**. Another barrier that a supplier can establish to deter termination by the customer is termination fees and costs. If the supplier can either establish high termination fees or create enough uncertainty as to how they are to be calculated, it can achieve a chilling effect on the customer's termination plans. If termination fees have to be accepted, then they should be set forth in terms of actual payment amount by service and by year in a schedule to the contract.

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