Giuseppina Fusco
Fabio Musso
(editors)

THE TECHNOLOGY TRANSFER CYCLE

linking societal needs and innovation

Proceedings of the Conference
Held in Urbino on
13th April 2018

Urbino University Press
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Giuseppina Fusco

Foreword

The present volume contains papers of the International Conference on technology transfer “The technology Transfer Cycle” held on 13th April, 2018 at the University of Urbino and organized by the Third Mission Office.

The principal aim of the conference was to provide the basis for a better understanding of the concept of the technology transfer cycle with a specific focus on the biomed and biotech reasearch fields, which includes the involvement of companies, rare genetic desease and oncologic patients and the market.

The invited speakers were asked to address the following main topics:

1) Understand how medtech companies intercept the needs of rare genetic disease patients and oncologic patients and consequently plan their research for product development in order to address these demands
   Are patients and their families effectively involved by companies in their research decision making process?
   At which stage farmaceutical companies consider patient engagement across the product lifecycle, from clinical development through product launch?
   Which are the benefits for companies that maximize direct patients engagement strategies?
2) Understand the ways through which research results reach the market to satisfy the needs of the patients affected by these patologies.
   How do medtech companies intercept University research results?
   Are patents an effective technology transfer mode from Universities to companies?

Which are the academic patent transfer modes to reach life science companies?
Which companies are interested in Italian University life science patents? How can they be identified?
How do research result reach the patients? Which are the benefits of the overall technology transfer cycle for patients?

The published papers are miscellaneous as they include researches carried out over the last few years on the topic addressed, reports based on the professional experience of the speaker in the field and a transcription of the speaker's slide presentation.

Esteemed readers, on behalf of the Prorector to the Third Mission, Professor Fabio Musso and of the Third Mission Office, we would like to express our deepest gratitude and appreciation to all speakers, participants and attendees for their valuable contributions. We sincerely hope that you shall take part in our future conferences held at the University of Urbino on technology transfer, with a new theme and innovative papers.

Finally, we would like to thank all of the proceeding team who have dedicated their support and time to bring these scratches into a book.

Loredana Guglielmetti [1]

What does a patent protect? Incentives for companies and public research institutes

An invention can be patented if it consists in a solution to a technical problem. To be patentable an invention must be also new, original, industrially applicable. Both products and processes/methods can be patented.

The patent is an exclusive right granted to applicants that, through the patent application, accept to publish the patent documents revealing the technical details of the inventions. Thus, it can be compared to a contract between the applicant and society: the applicant receives from society the exclusive right to prevent third parties from producing, using, selling, or importing the object protected without patent owner's consent (and, in case of processes, the exclusive right to prevent third parties from applying the process, using, selling, or importing the product obtained by a protected process). Society receives from the applicant the knowledge not yet available to experts in a whole range of technical fields.

Patent rights have a specific territorial validity, and a time limit that is a maximum of 20 years for inventions and 10 years for utility models.

But a granted patent is not a guarantee of commercial success; to obtain substantial advantages a patent should be effectively exploited. This can be done whether through direct exploitation (producing, selling, etc..), licensing contracts, research and development co-operations/agreements, and other possible means necessary to fully exploit the potential of the exclusivity rights given by patent.

As major drivers of innovations, patents are included in the so called "intangible assets" of enterprises that, as know-how, trademarks,

[1] Head Division VII, National and European Patents, International applications, Ministry of Economic Development, Directorate for the Fight Against Counterfeiting (The Italian Patent and Trademarks Office, Italy).

industrial design, and so on, nowadays create economic value for enterprises more than tangible assets.

In a fast changing economy, based on intangibles, with growing competitiveness, Governments are subjected to increasing pressures to foster technological and economic capabilities of the enterprises. As intellectual property is one of the main assets for a firms' competitiveness, providing incentives for innovation, promoting and supporting the protection and use of intellectual property; in particular, the patenting activities, as well as promoting the enforcement of IP-related rights are priorities of all policy-makers facing global economic challenges.

Patent related incentives/subsidy programs in Italy

In Italy different policy measures were adopted in order to promote and support patent filings and their exploitation. From 2007-2008 the Italian Patent and Trademark Office (UIBM) began to implement a long-term program aimed at fostering patenting activities, especially of Italian small and medium-sized enterprises. The program consists of different measures whose final goal is to enhance and strengthen the effective protection and use of patents by Italian inventors and enterprises by:

- the introduction of 'novelty search' in the Italian patenting procedure,
- patent related incentives and subsidy programs, such as subsidies for patent filings and incentives for business use of patents,
- programs of staff support of University technology transfer offices.

Novelty search for Italian patent applications

Since 2007, specific laws were adopted to introduce the 'novelty search' in the Italian patenting procedure: in particular, the Ministerial Decrees 3.10.2007 and 27.6.2008, which established also that the European Patent Office is the official Authority for carrying out the 'novelty search' for Italian patent applications. According to Italian law all first filings are submitted to 'novelty search', and only applications claiming a domestic or foreign priority are excluded.

The Italian Law was mirrored by a specific Working Agreement between the Italian Government and the European Patent Organization (EPO), signed in June 2008, that established that 'novelty search' is carried out by the EPO examiners for Italian patent applications filed from 1st July 2008, according to the European rules and guidelines for examination. The search report is issued within 9 months from the date of filing of the patent application, or before the expiry of the year to file a new patent application (a European or International application or a national application in foreign IP Offices) claiming the Italian priority. According to this system, almost 8.000 Italian applications per year are submitted to 'novelty search' and obtain the corresponding search report.

It was also established that for patent applications filed with UIBM the 'novelty search' is paid by the Government, and as such, it is a powerful tool for financially supporting the efforts of Italian applicants, in particular SMEs, in their patenting activities.

The aims of the introduction of the new procedure are actually various: basically, an increase of Italian patent filings, but also the improvement of patents' quality (patents granted with 'novelty search' have stronger legal requirements and cannot easily be challenged in Court), and the increase of Italian patents extended to European or International applications.

Effective results were acquired in terms of patents' quality and increase of patent filings both with Italian Office and with International and European Patent Offices. It is evident that the new Italian patenting system, based on 'novelty search', has proven to be a great support for SMEs to exploit patents and to enlarge the scope of their business.

Patent related incentives and subsidy programs. 'Brevetti+' and 'Brevetti+2'

In 2009 the so called «*Pacchetto Innovazione*» was launched to support SME's business based on patents.

Within this program, specific incentives called 'Brevetti +' and 'Brevetti +2' were initiated and implemented by the UIBM and INVITALIA (a national agency, owned by the Italian Ministry of Economy), the latter was delegated to implement the measures.

'Brevetti+' was divided in 2 different sub-measures:

1.subsidies for patenting ;

2. incentives for business use of patents.

The ***'Subsidies for patenting'*** are aimed at raising the number of national filings and the extension of them to European or International filings. The Call for Application requires the possession of some specific pre-requisites: being an Italian SME with a patent or patent application filed with UIBM from 01.01.2011; a positive search report carried out by EPO.

The grants allowed range from € 1500 up to € 6 000. Additional grants are allowed if other specific conditions are met:

filing of one or more international applications according to Patent Cooperation Treaty (PCT) claiming the priority of an earlier Italian application, Filing of a European Patent Application at EPO claiming the priority of an earlier Italian application, Application extended to PCT countries and, in particular to specific countries, such as China, India, USA, Brazil and Russia.

On the other hand, the measure "***Incentives for business use of patents" is*** more complex and broader than the "Subsidies for patenting"; aiming to help SMEs to give economic value to their patents and improving enterprises competitiveness through the economic exploitation of patents. The Call for Application requires the possession of the following specific pre-requisites:

- Eligible Italian SME with a patent or patent application or patent license,
- Italian Patent Application Filed with UIBM from 01.01.2011,
- Positive Search Report carried out by EPO in case of Italian Application,
- Request of substantial examination in case of European Patent Application or International (PCT) applications that claim the priority of an earlier Italian application.

In 'Brevetti+' grants of up to € 70 000 are awarded to SMEs to cover the 80% of the maximum allowed costs for buying and paying the specialist services necessary to economically exploit the patent.

Under 'Brevetti+2' (launched in 2015) the maximum amount of incentives that can be awarded for each SME is € 140,000 for supporting business use of patents and, in particular, the productivity and market development of SMEs and the improvement of their competitiveness based on patent rights exploitation.

The pre-requisites required for the sub-measure 'Brevetti+2' are mainly the same as Brevetti+ Incentives for business use of patents:

- Eligible Italian SME with a patent or patent application or patent license
- Italian Patent Application filed with UIBM from 01.01.2013
- Positive search report carried out by EPO
- University/academic Spin-off with specific conditions

As mentioned, in 'Brevetti+2' grants of up to € 140 000 are awarded to cover 80% of the maximum allowed costs, whereas for academic spin-offs up to 100% of allowable costs can be awarded.

As in the other sub-measure, the incentives can cover the expenses for buying and paying the specialist services necessary to economically exploit the patent. The specialist services that can be financed concern, for example, industrialization and engineering, technology transfer, organization and development, marketing.

To obtain the incentives it is necessary firstly to present a precise Project Plan with valid and measurable outcomes.

The measures included in 'Brevetti+' were open for SMEs from 2nd November 2011 until 2th December 2015. The measure 'Brevetti+2' was open from 6th October to 2nd December 2015.

In that period 4277 applications were submitted.

The figures are summarized in the table below:

	Subsidies	Incentives	Brevetti +2	Total
Submitted Applications	2.930	1.165	182	4277
Applications not complying with pre-requisites/not accepted	878	607	92	1.577
Applications accepted	2.052	558	90	2.700
% accepted	*70%*	*48%*	*50%*	-

Source: Invitalia, processed by UIBM.

The figures presented highlights the higher acceptance rate for the subsidy measure whose pre-requisites were less strict, whereas for more complex incentives programs, tied to a concrete business plan for economic exploitation of the patent right, the percentage rate of acceptance was lower.

The enterprises that participated in the subsidy and incentives programs work in a large variety of sectors of the economy, producing and using a wide range of new technologies.

In the following table the distribution of the participating SMEs' product fields are shown:

Product field of the SME with project accepted	subsidies	Incentives	Brevetti +2	Total SMEs
Trade	193	49	7	249
Buildings	63	20	6	89
ICT	315	131	16	462
Services to SMEs	286	75	13	374
Other fields	10	2	1	13
TOTAL	**2052**	**558**	**90**	**2700**

Source: Invitalia, processed by UIBM.

Subsidy programs for universities and research institutions

In recent years, specific subsidy programs based on intellectual property for universities and research institutions were implemented by UIBM. In 2015 a program for supporting the capacity building of University Technology Transfer Offices was established. In particular its purpose was to strengthen and motivate staff and to improve their skills focused on technology transfer, the exploitation of intellectual property rights, and improving relationships with the industrial sector.

In 2018 a new project in cooperation with the University sector is being implemented. The project's goal is the creation of a web platform for knowledge-share in which to encourage technology transfer and commercialization of research results.

Conclusion

Intellectual property, and patent rights in particular, contributes to the economic and social development of all countries. The public administrators play an important role in implementing industrial policy instruments, such as subsidies and incentives programs to enhance patent protection, enforcement and economic exploitation. There is a wide range of policy tools for pursuing this goals: from short-term programs to mid to long-term strategies of patent related incentives . Whereas the short-term programs generally require less strict pre-requisites for obtaining subsidies because the main goal is to increase the patent filings; the mid to long-term strategies consist of more complex incentives programs aimed at improving the quality of patent and supporting SMEs and individual inventors in their capacity to create business and economic value from patent rights.

The Italian Office (UIBM) has chosen a mix of strategies, as illustrated in the UIBM incentive/subsidy programs. At the start of the programs it was necessary to strengthen the Italian patent system and to build awareness of the importance of patenting. Greater importance was then placed on favouring and supporting the economic exploitation of patent rights. As in many other countries in Europe, Italy considers patent and intellectual property as a key factor in stimulating innovation and technology enhancement with its final purpose to maximize the benefits the patent system can bring to the economic system as a whole.

Mariagrazia Squicciarini[2]

Innovation and technology transfer: the role of IP (*)

«The **OECD** (Organisation de coopération et de développement économiques) is a unique forum where the governments of 30 democracies work together to address the economic, social and environmental challenges of globalisation. The OECD is also at the forefront of efforts to understand and to help governments respond to new developments and concerns, such as corporate governance, the information economy and the challenges of an ageing population. The Organisation provides a setting where governments can compare policy experiences, seek answers to common problems, identify good practice and work to co-ordinate domestic and international policies» (OECD Principles and Guidelines for Access to Research Data from Public Funding-2007).

Throughout OECD member countries, growing quantities of data are collected by publicly-funded researchers and research institutions. Amongst the data collected and analysed by OECD interest is placed on intellectual property reports.

What is intellectual property and what are IP rights?

Intellectual property refers to creations of the mind: inventions, literary and artistic works, and symbols, names, and images used in commerce. Intellectual property is divided into two categories.

1) Industrial property includes patents for invention, trademarks, industrial designes and geographical indications.

2) Copyright covers literary works (such as novels, poems and plays), films, music, artistic works (e.g. drawings, paintings, photographs and sculptures) and architechtural design.

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[2] Senior Economist, Head of Unit, Head of Microdata Lab, Patent Expert (OECD, Organization for Economic Co-operation and Development, France).

(*) The following is a transcription of the speaker's slide presentation.

What are intellectual property rights?

Intellectual property rights are like any other property right. They allowe creators, or owners, of patents, trademarks or copyrighted works to benefit from their own work or investment in a creation.

Why promote and protect intellectual property?

There are several compelling reasons. First, the progress and well-being of humanity rest on its capacity to create and invent new works in the areas of technology and culture. Second, the legal protection of new creations encourages the commitment of additional resources for further innovation. Third, the promotion and protection of intellectual property spurs economic growth, creates new jobs and industries, and enhances the quality and enjoyment of life.

What is a patent?

A patent is an exclusive right granted for an invention – a product or process that provides a new way of doing something, or that offers a new technical solution to a problem.

A patent provides patent owners with protection for their inventions. Protection is granted for a limited period, generally 20 years.

What kind of protection do patents offer?

Patent protection means an invention cannot be commercially made, used, distributed or sold without the patent owner's consent. Patent rights are usually enforced in courts that, in most systems, holds the authority to stop patent infringment. Conversely, a court can also declare a patent invalid upon a successful challenge by a third party.

Striking the right balance: appropriability vs technology diffusion

To get policies right we need precise questions and robust evidence.

To design effective and non-distorsive policies 2 questions are key: 1) what is that we know "for sure", for which robust (i.e. casual) evidence exists? Less than we would have liked to: studies exist (especially on patents), but often get at correlations, are country-specific, …2) what is that we do not know and would need to know? A lot (e.g. IP bundles, IP quality and value, IP systems' features,…). Data often an issue.

Patents and cumulative innovation: causal evidence.

"Patent rights facilitate or impede follow-on innovation?"

- Galasso & Schankerman, QJE 2015:

Studies causal effect of removing patent rights by court invalidation on subsequent research related to the focal patent, as measured by later citations.

Finds invalidation leads to 50% increase in citations to focal patent, on average.

Impact is heterogeneous and depends on bargaining environment: Patient rights cblock downstream innovation in computer, electronics, and medical instruments; not in drugs, chemicals, or mechanical technologies.

Effect driven by invalidation of patents owned by large patentees that triggers more follow-on innovation by small firms.

Patents and cumulative innovation: causal evidence

- Galasso & Schankerman, RAND 2018:

Studies causal impact of patents on subsequent innovation by the patent holder.

Finds invalidation leads to 50% decrease in patenting by the patent holder, on average.

Impact depends on characteristics of patentee and competitive environment: effect driven by small innovative firms in technology fields where they face many large incumbents.

Invalidation of patents held by large firms does not change the intensity of their innovation but shifts the technological direction of their subsequent patenting. Patents and the market for ideas.

Patents may play a role with regard to:

- Signalling and reducing asymmetric information;

- Reduce uncertainty (e.g. Czarnitzki and Toole, 2011, find patents to reduce the effect of market uncertainty on the firm's investment decision);

- Attracting finance (e.g. Hall, 2018, for a survey; Useche, 2014, finds significant and robust positive correlations between patent applications and IPO performance);

- Timing of cooperation (e.g. Gans et al. 2009. The likelihood to achieve a cooperative licensing agreement between start-up technology entrepreneurs and established firms significantly increases after patent allowance)

- Trade (e.g. Maskus, 2016. There could be an important complementarity between the formation of trade agreements and their IPR standards)

-Salvage value (e.g. Hall, 2018)

The role of technology transfer offices

TTO, aka Technology Licencing Offices (TLOs) are meant to act as channel between academia and industry.

«while technology transfer may have several objectives, depending on the resource, user of mechanism, the main objective is to promote movement of federally developed ideas, knowledge and technologies created in the public institutions to the marketplace for commercialization» Audretsch et al. (2014)

They help bring research developments to markets, and are responsible for technology transfer and other aspects of the commercialisation of reasearch taking place in universities/Research Centres.

TTO and the mission of Universities

“There are key underpinnings required to promote success in knowledge-based economic development: creating the highly-trained human capital that industry requires; and capitalizing on reaserch by converting it for private-sector application.

Creating human capital and conducting reaserch, along with its efficiency as measured by output (patents, licenses executed, licensing income, and startups) relative to input (reasearch expenditures), depict the production of good universities delivering on their mission”. Source: DeVol et al. (2017) “Concept to Commercialization: The best Universities for Technology Transfer”, Milken Institute.

Micro-data Lab

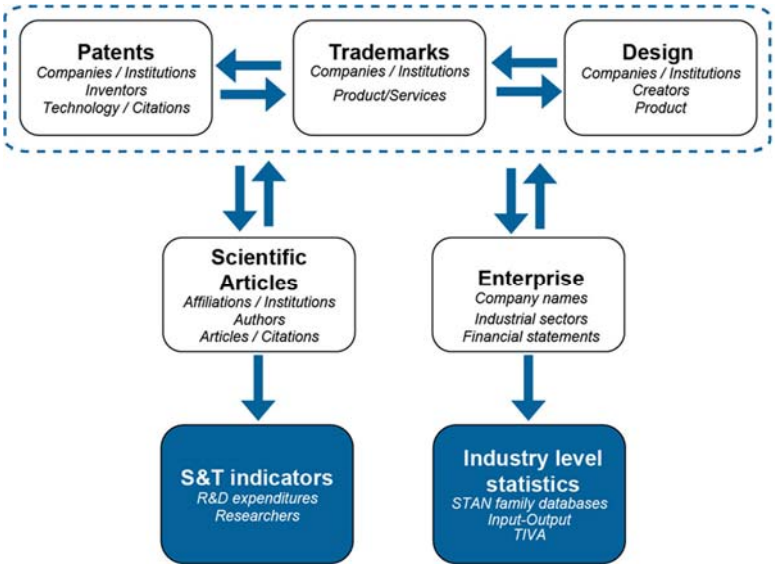
“Micro-data Lab is a long term data infrastructure project of the OECD Directorate for Science, Technology and Innovation (STI). It

supports microdata-based methodological, statistical and analytical work of many OECD Committees) and collects and links large-scale administrative and commercial micro-level datasets. These mainly relate to administrative data such as intellectual property (IP) assets, including patents, trademarks and registred designs; scientific publications; and information on companies from private providers.

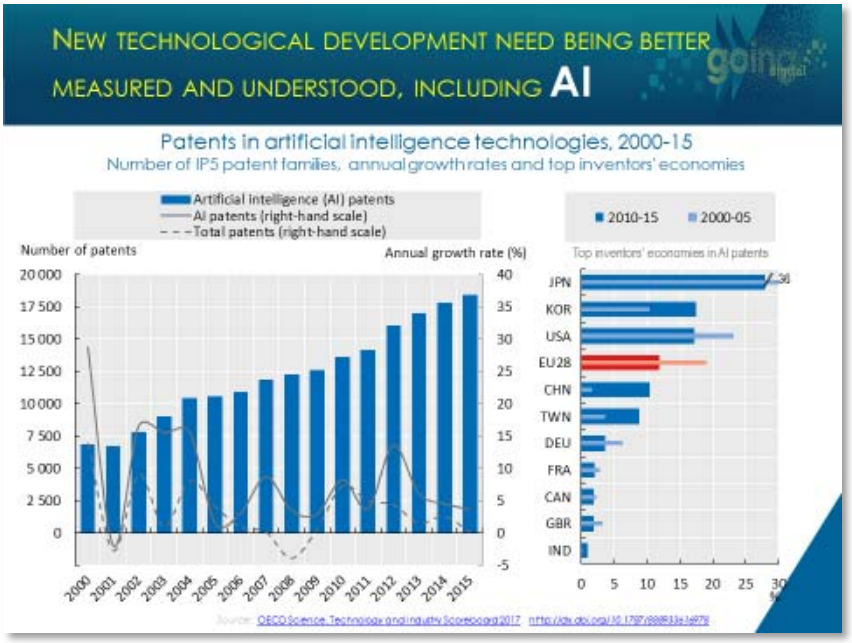
These micro-data, which complement and enhance official statistics like macro-aggregates or survey-based data, have the advantage of being granular in nature and comprehensive in time and geographical coverage

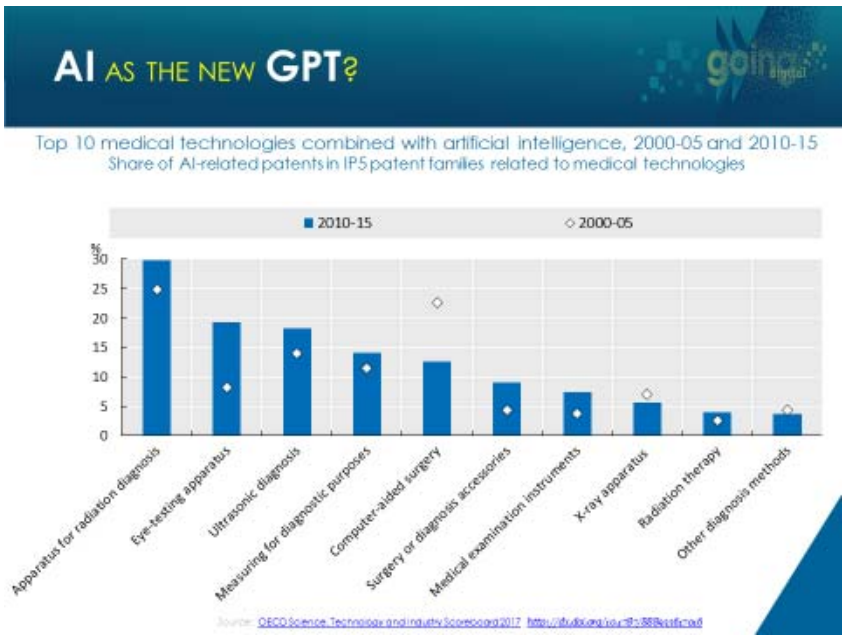
By providing detailed information about the behaviour of economic agents and the way science and technology develop, these data help address policy-relevant questions, such as those related to the generation and diffusion of new technologies, the different ways in which firms innovate, science-industry links, researchers' mobility patterns or the role of knowledge based assets in firms' economic performance.

The STI Micro-datalab is open to visiting researchers. Access is granted free of charge upon submission of a formal request" (wwe.oecd.org/sti).



Sources may be used in an indipendent fashion, e.g. to develop specific indicators; or combined to augment the quantity and quality of the information.





Mauro Magnani[3]

University Knowledge transfer

The University of Urbino features important cases of valorization of research results.

Case 1 - EryDel SpA: translating innovation into a cure

EryDel S.p.A. (www.erydel.com) was founded by Prof. Mauro Magnani and Prof. Luigia Rossi, both from the University of Urbino, Italy, in 2007 as a university *spin-off* with the aim of developing the technology of drug delivery based on the use of autologous erythrocytes.

The research originated from the lab bench of the laboratories of the University of Urbino when professor Magnani was making his studies for his graduate thesis based on the biochemistry, fisiology and biology of red blood cells. The idea that this peculiar cells have a number of properties that can be conveniently used for a number of applications was quickly foreseen. In particular it was envisaged that erythrocytes could be used for example both for the diagnosis of specific patologies and as means of incapsulatation and delivery of drug or other agents. Indeed the same idea was already circulating amongst research groups in France and United States at the time.

The group greatest interest was anyway focused on working with red blood cells to deliver drugs into the circulation Red blood cells (RBC) are ideally suited to perform as delivery systems having properties that define most of the wanted characteristics of drugs, theranostics and diagnostics carriers. These carriers, initially explored for the administration of enzymes to patients with genetic defects in the late 70^{s}, have been shown to be able to carry peptides, proteins, small molecules, nucleic acids, antibodies and a large number of nanomaterials.

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[3] Full Professor of Biochemistry and Director of the School of Biology and Biotechnology (University of Urbino, Italy).

The research group found, moreover, that RBC can be engineered also by coupling agents on their external surface (proteins, antibodies, peptides, nanoparticles) for targeting to selected districts or exposed molecular targets on the vascular endothelia. Targeting of drug-loaded RBC can be obtained also by inducing red cell membrane modifications that mimic the exposition of a red cell senescence antigen which is known to result in red cell removal from circulation by tissue macrophages. RBC can also be engineered as antigen delivery systems and/or as immunomodulatory agents to induce tolerance.

Once obtained the first results the research group decided to implement these data starting collaborations with companies to translate the idea into a product.

In 1996 the research project starts as a collaboration between Dideco R&D group and the Institute of Biological Chemistry, Prof. Mauro Magnani and his Group, at the University of Urbino.

In 1997 Dideco files a patent on the RBCs drug encapsulation and targeting in Europe, USA and Japan and Magnani was one of the inventors. The medical device developed involve the transient opening of RBC under controlled condition, the encapsulation of desired agent(s) and the subsequent resealing. The resulting drug-loaded RBC, identical to the native one, are then administered to a patient in need. This can be done with autologous blood. A patient gives just 50 of blood and then receives his blood back with the drug inside.

The following research studies were carried on:

1999 First Pilot Study on COPD patients, using RBCs encapsulated with dexamethasone 21-P, a cortico-steroid drug (Published 2001).

2000 Pilot study on Cystic Fibrosis (Published on 2004). In 2004 EMEA granted to Dideco Srl “Orphan Drug” designation for “Dexa 21-P incapsulated into autologous RBC for treatment of Cystic Fibrosis.

2001 Pilot study on Inflammatory Bowel Diseases (Published on 2005).

Companies sometimes, especially the large ones, have priorities that are different from the ones university researchers have. It happened that the patent was not developed in the way the inventors would have expected from the company, so inventors negotiated with the company

to receive back the patent already granted in US, Europe and other countries included Japan at the time.

In 2007 EryDel SpA was founded by professor Magnani and professor Rossi as a *spin-off* of the University of Urbino and Dideco granted to EryDel un-resctricted license on the IP properties. The aim of Erydel foundation was to develop the technology described by the patent.

At present the company is totally supported by venture capital companies, so far the investment is around 30 million euros, and the company is run not by academics but by people coming from other companies, with an experience with that. After 5 years of working, in 2013, Erydel was nominated among the top 5 most innovative EU enterprises.

The key business of Erydel is still based on the discoveries professor Magnani and professor Rossi developed at the University of Urbino many years ago on the possibility of modifing the red bood cells for encapsulating drugs and other materials.

EryDel SpA is today a biotechnology company specialized in the development of drugs delivered through autologous red blood cells (RBCs) by using a proprietary medical device technology particularly dedicated to developing first-in-class therapeutics and life changing therapies for patients with rare disorders,

As reported by the Chief Executive Officer, Luca Benatti "its most advanced product, EryDex System (EDS) is under late stage development for the treatment of Ataxia Telangiectasia, a rare autosomal recessive disorder for which no established therapy is currently available. EryDex has received Orphan Drug designation for the treatment of AT both from the FDA and the EMA. A completed pilot Phase II trial in AT patients demonstrated statistically significant efficacy of EDS on both the primary and secondary efficacy measures. An international multi-center, Phase III pivotal study, ATTeST, is being conducted. EryDel has a pipeline of preclinical programs that use its proprietary RBC's delivery technology for the treatment of other rare diseases."

EryDel technology has also been proven to be effective in delivering contrasting agents both in magnetic resonance imaging (MRI) and in fluorangiograpy. A new patent in this field, generated by researchers at

the University of Urbino under the umbrella of EU FP6 project named NACBO, has also been transferred to EryDel.

Case 2 -DIATHEVA S.r.l.: the research can be profitable

DIATHEVA S.r.l., is an Italian biotechnology company located in Fano (PU), founded in 2002 by researchers of the University of Urbino in Italy and angel investors.

As a spin-off of the University the mission of DIATHEVA was to translate research began at the University into industrial products through collaborations with industry partners as well as private research institutions.

The constitution of DIATHEVA was moved by a simple consideration that came from the work experience of the researchers : at the University of Urbino and in a number of public institutions there is a really excellent production of new ideas, potential new products and also reagents that have a big problem to be translated into commercial products. This is partially due to the fact that the mentality of researchers belonging to public institutions is different from the mentality of companies and regulatory authorities , consequently reserachers do not often have the right approach for the development of their products. It is necessary therefore for University researchers to work with people with experience in commercial product development if they do not want to loose time, their product and they do not want to loose the possibility to reach the final goal. The development of an idea is strictly depended on people.

A second issue is that researchers need to convincingly provide information about the inventions derived from their studies to potential investors or to other companies that can be interested in getting licence of their patents. It should be considered that some companies may support research further after licencing the patent because inventors are the most reasonably experienced person that can have information and knowledge for further development. It is important then that researchers be ready to continue to collaborate with companies as this can create a potential opportunity for people that want to invest on new ideas to have a drug product brought to the market.

DIATHEVA focuses on development, production and marketing of new and innovative products for diagnostic, research and therapeutic applications in the field of: cancer, microbial infection and pharmacogenetics, providing a wide range of reagents and kits for HIV-I study, pharmacogenetic tests for personalized and predictive medicine and innovative solutions for food safety.

Since its foundation, DIATHEVA has been investing many resources in R&D activities: in particular the company has applied with success to many funded European and national research projects enlarging its collaborative and commercial network and acquiring an updated know-how.

- In 2005 DIATHEVA obtained the first European funds for a project concerning the development of innovative AIDS vaccine based on rHIV-1 Tat protein;
- In 2006 DIATHEVA obtained further European funds for the development of new methods and tools for diagnosis of human pathogens. Thanks to this project DIATHEVA created the innovative "MULTIPATHOGEN" platform for the identification of food-borne pathogens;
- In the same year DIATHEVA acquired a facility for the production of recombinant proteins GMP grade for clinical and pre-clinical trial studies;
- In 2007 DIATHEVA signed the first contract of manufacturing with the Italian Institute of Health for the production of recombinant HIV-I Tat GMP grade. The protein was used in a Phase I/II clinical trial;
- In 2008 DIATHEVA obtained the quality certificate ISO9001-2008 for all commercial, production and quality processes;
- Since 2009 DIATHEVA has been directing its own interests on the discovery and development of biologics with diagnostic and therapeutic potential, in the fields of cancer and virology;
- In 2009 in collaboration with other biotech firms in the Marche Region DIATHEVA founded Marche BIOTECH, an independent, non-profit association with the aim to promote the bioscience industry in

Italy, to expand the knowledge and expertise of Marche's business, concerning the life sciences.

In 2012, the SOL Group acquired a majority stake in DIATHEVA and has since continued to invest in the company's operations. SOL is an Italian multinational group which operates in Europe applied research and marketing of technical, pure and medicinal gases and in respiratory home care and employs 3,000 people in 26 countries.

At present DIATHEVA continues to have a diversified range of activities, its main business model is based on development, manufacturing and marketing of innovative diagnostic kits. The company has also signed several R&D and GMP manufacturing contracts with Italian and foreign companies.

DIATHEVA has a GMP facility, authorized by AIFA, to produce and release APIs for pre-clinical and clinical trials with a special emphasis on new immunogens against HIV and other microbial pathogens.

DIATHEVA has two promising anti-cancer single-chain fragment variable (scFv) antibody in preclinical trial studies and one scFv antibody for the treatment of Candida Albicans in discovery.

The company has the experience, expertise, capacity, and flexibility to serve as strategic partner for drug development and manufacturing needs.

Marta Catarino[4]

Academic patent transfer modes: the experience of TecMinho - Technology Transfer Office of University of Minho, Portugal

Abstract.
In the process of supporting the transfer of promising research results to the market, Knowledge Transfer Offices focus on guaranteeing a solid patent application, effective due diligence and outlining the expectations for the outcome of the process. There are, however, different routes to market to chose from. Is this going to be an exclusive license to a multinational company, a non-exclusive license to a local company or an assignment to a spin-off company? We will explore the different scenarios and share lessons learnt from the different strategic options that can help a Knowledge Transfer Office optimise the impact of their proprietary results
Keywords: Knowledge Transfer, Patenting, Licensing, Spin-offs

Introduction

The Knowledge Transfer Study (ISBN 978-92-79-32388-1, accessible at www.knowledge-transfer-study.eu), developed by the Directorate General for Research and Innovation of the European Commission in 2013, demonstrates the gap between the performance in knowledge transfer by US vs EU Knowledge Transfer Offices (KTOs):

- 2/3 of universities report that their licensed technologies resulted in at least one commercially successful product or process in the previous 3 years;
- the top 10 universities earn approximately 85% of all license income;
- 88,8% of €346M in reported license income is from biomedical inventions;
- European universities outperformed US in amount of research expenditure required to produce one patent grant, start up and license

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agreement, but US outperforms at producing invention disclosures, patent applications and license income;

- license income in Europe equals 1,5% of the research expenditures, while in the US license income equals 4,5% of research expenditures.

Furthermore, the main objectives identified by KTOs are:

- to generate possibilities for research collaboration;
- to promote the diffusion of science and technology;
- to generate revenues for the host institution (University or other Public Research Organisation).

These insights into the nature of Knowledge Transfer, more than the difference between the US and EU, reflect the challenges that KTOs face when supporting the valorisation of research results from Public Research Organisations. While the mission of the KTO is highly focused on non-profit areas, such as the diffusion of science and technology, faculty service through greater visibility, dissemination of research results, awareness and capacity building initiatives for researchers, it is expected that the activity itself is sustainable or even profit-generating.

This affects the decision-making process of defining routes to market: what are the benefits of licensing vis-à-vis setting-up a spin-off for the exploitation of a patented research result?

Difference between transfer modes

It is essential for the KTO to clarify with their management (the host institution - University or other Public Research Organisation) their specific mandate. The main operational differences mostly focus on a) Faculty service, b) Profit generation.

a) Faculty service:

KTOs are expected to provide added-value services to faculty in the area of KT, such as organising meetings between researchers and industry, recognising and disseminating the impact of research, actively contributing to University seminars, courses, workshops, publication of "how to" guides in industry relations, providing legal support in managing industry finding, and allowing enough freedom for

researchers to get involved in collaborative research, problem solving, and other initiatives with industry.

Main characteristics in activities aimed at providing faculty service include:

- raising awareness
- each disclosure raises the same interest
- researcher's objectives and profile are key
- many researchers are happy for this service

b) Profit generation:

KTOs are expected to be sustainable, and even to bring profit for the University or PRO. While several studies and surveys indicate that a profit from KTO activities is unlikely to be achieved, a certain degree of self-sustenance is expected from KTOs.

Main characteristics in activities aimed at generating profit include:

- focus on profit
- pressure to concentrate on potentially profitable disclosures
- focus on biomedical sciences as most likely to provide profit
- professionalisation of the KTO team in business-oriented activities
- very few researchers are happy with this service: only the few "profitable" ones.

A combination of these two perspectives is possible. However, a focus on one of these different approaches affects how decisions are taken regarding the different strategies and routes-to-market in the sinuous path of bringing innovative, proprietary research results from academia to the market.

Main drivers for decision making regarding whether to license or create a spin-off include:

- team profile: competencies, commitment, motivation
- time (and cost) to market: expected investments in human resources, time and funding to fully validate the proof-of-concept and business plan development, proven Technology Readiness Level

- access to angel or venture capital and legal requirements for establishing an academic-based private company
- market context: competitor landscape, potential monopolies, barriers to market entry.

The assessment of these drivers requires a professional approach to knowledge transfer and business planning for R&D results. Experienced KTOs are key to a successful and sustainable activity.

Maturity of Knowledge Transfer Offices

The level of support KTOs can provide to researchers, and an evidence-based decision regarding an exclusive or non-exclusive license, the partner profile, the field and geographical limitations of licenses, or options such as establishing a new technology-based venture, will depend on the experience and maturity of the KTO. Aspects such as previous experiences, track record, team competencies and capacity, established methodologies and processes, will influence the decision. It is relevant for KTOs to understand their positioning in terms of maturity and plan for continuous improvement. As an example, the following table indicates different levels of maturity for KTOs, including in terms of staff capacity and competencies, experience as an office, and institutional framework.

Most KTOs depend on external advice, such as through an Intellectual Property or Innovation Committee, and autonomy in decision-making would require a positioning in terms of maturity closer to levels 4 or 5 in the Maturity Framework (table 1).

Conclusions

The decision process regarding the transfer of patented research results to the market must take into account several aspects. While the process of scouting, identifying, early-stage assessment of commercial potential and patentability require significant resources from KTOS, the decision regarding the different exploitation routes available is essential to the success of bringing new products, processes and services to the market, and to society as a whole.

Beyond patenting results which are simply patentable, KTOs focus increasingly in identifying the added value and opportunity for commercial exploitation of research results. This requires an understanding of the technical feasibility, market opportunity and business potential of such results. KTOs are essential in providing this support to researchers and potential academic entrepreneurs, and a higher level of maturity in human resources, office experience and institutional support can greatly improve the expected outcomes.

Table 1

	KT MATURITY FRAMEWORK	Level 1	Level 2	Level 3	Level 4	Level 5
Staff	TT Staff Experience	TT activity new to RPO, no dedicated TT/KT staff.	TT/KT staff at early experience level.	TT/KT staff with developing expertise and skills.	Staff at RTTP or equivalent.	Highly experienced and skilled TT/KT staff mix.
Office	Spin-outs / LOA Activity	Very low, sporadic and unplanned activity.	Developing TT output, first LOA deals, some spin-out possibilities.	LOAs regular and planned, emerging pipeline of spin-outs.	Several years' experience in LOA and HPSU type spin-out creation.	Large portfolio of deal experience. Well-developed activity pipeline.
	Industry Engagement	Emerging industry engagement.	Pockets of industry engagement.	Good industry engagement across several research groups.	RPO wide targeted industry engagement.	Large portfolio of RPO wide industry contracts.
	Consultancy Activity	No institutional consultancy strategy, private capacity only.	Pockets of RPO administered and planned consultancy.	RPO wide policy and mechanism for consultancy.	Managed and marketed consultancy offering by RPO.	Significant and mature consultancy activity across RPO.
	TT / KT Culture	TT/KT culture not well established.	TT/KT culture accepted at management and researcher level.	TT/KT activity considered in staff promotion evaluation.	RPO wide recognition that TT/KT activity is an important activity.	TT/KT embedded as core RPO activity along with teaching and research.
Institute	IP Management Processes	RPO IP management policies not in place.	First version policies relating to LOAs and spin-outs in place.	Developed IP and campus company policies.	First RPO wide processes for IP Management as per IP Protocol.	RPO broad IP management developed and monitored.
	Transaction Speed and Quality	Institutional inexperience in TT/KT activity.	TT/KT contract negotiation laborious and time consuming.	TT/KT contract negotiation slow due to multiple review / sign-off.	TTO has remit to negotiate and sign off on all TT/KT deals.	Very efficient and effective TT/KT transactions.

Knowledge Transfer Maturity Framework,
Scanlan, J. - Maynooth University, 2016.

Roberto Moro Visconti [5]

Patents Economic Evaluation

Abstract
Patents are the result of risky and costly R&D and the developer will try to recover its costs (and earn a return) through the sale of products covered by the patent, licensing others to use the invention (often a product or process), or through the outright sale of the patent.
Patents are typically valued for litigation or licensing purposes.
This paper shows how patents can create scalable value, levered by debt and serviced by intangible-driven incremental EBITDA and cash flows. Intangibles like patents are also a vital component of cash generating value and goodwill as an excess return. Operating leverage is enhanced by scalability, with a positive impact on cash generation.

Keywords: intangible valuation; EBITDA; cash flows, information asymmetries; royalties; market value; technology transfer.

JEL codes : O32, O34 ; G31, G17

1. Patents: definition and rationale

A patent is a limited monopoly that is granted for 20 years in return for the disclosure of technical information (Benty & Sherman, 2014, p. 375).

A patent is a set of exclusive rights granted by a sovereign state or intergovernmental organization to an inventor or assignee for a limited period of time in exchange for detailed public disclosure of an invention. An invention is a solution to a specific technological problem and is a product or a process (WIPO, 2008). The word patent originates from the Latin patere, which means "to lay open" (i.e., to make available for public inspection).

Patents are usually the result of risky and costly research and development and the developer will try to recover its costs (and earn a

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return) through the sale of products covered by the patent, licensing others to use the invention (often a product or process), or through the outright sale of the patent.

The very fact that costs are incurred mainly before patentability for inventions may well have important transactional implications: patents are ripe for sale or licensing even immediately after registration, considering also their finite useful life, with typically soon peaking and then declining values. Terminal value of an expiring patent is not necessarily zero, if it can still be used as a distinctive, albeit no more protected, invention, during and after its phase out.

The protection provided by a patent is limited to 20 years, and so is shorter than the protection of copyright law or trademark registration, but the rights are more extensive, and cover most commercial uses.

Patents are granted only after a long registration process. Patent rights help enterprises keep unique competitiveness in the market, under protection of law, avoiding the copying and plagiarism of other competitors (Danchev, 2006).

Justifications and economic rationale for patents derive from:

- The natural right of inventors to the proceeds of their mental labour;
- The grant of a reward for inventive activity that otherwise would lack proper incentives.

Patent valuation is required in many cases as:

2. M&A operations, spin-offs, demergers, joint ventures, etc.;
3. Bankruptcy;
4. Sale or license;
5. Patent conflicts and disputes;
6. Collateral for bank loans;
7. Accounting;
8. Taxation (transfer pricing; patent box, etc.).

2. From Know-How to Patents

"Know-how and trade secrets are proprietary information or knowledge that assists or improves a commercial activity, but that is not registered for protection in the manner of a patent or trademark" (OECD, Transfer Price Guidelines, § 6.5., 2017).

"Know-how is practical knowledge of how to get something done, as opposed to «know-what» (facts), «know-why» (science), or «know-who» (networking). Know-how is often tacit knowledge, which means that it is difficult to transfer to another person by means of writing it down or verbalizing it. The opposite of tacit knowledge is explicit knowledge. In the context of industrial property (now generally viewed as intellectual property), know-how is a component in the transfer of unpatented proprietary technology in national and international environments, co-existing with or separate from other Intellectual Property rights such as patents, trademarks and copyright and is an economic asset" United Nations Industrial Development Organization, (1996).

Know-how (to do it) is a key and trendy factor behind competitive and comparative advantage (Hall, 1993), representing the invisible glue behind strategies of product differentiation and innovation, creating ancillary value from other factor inputs.

If comprehensive added value may be compared to an iceberg, know-how may well represent its gravitational sunk part.

3. Accounting of Intellectual Property as a pre-requisite for valuation

Definition (Mehta & Madhani, 2008), accounting treatment and the consequent valuation of intangible capital are a prerequisite for financial performance appraisal and consequent bankability, combining economic margins, such as EBITDA, with debt-servicing cash flows.

The slippery nature of intangibles and their consequent uneasy valuation boundaries represent a well-known problem.

IAS 38 (Para. 12.) defines an intangible asset as "an identifiable non-monetary asset without physical substance". Whatever is not identifiable is allocated in (residual) goodwill, an Arabian phoenix for accountants.

"The academic and professional interest in Intangible Capital is underpinned by the idea that it can be considered one of the main levers to create value" (Giuliani, 2013) and, according to Michael Porter's fundamental insights, value creation derives from lasting competitive advantage over rival entities, embedded in continuously innovating business models, to be properly designed and managed. Competitive edge is increasingly driven by the catalyst presence of intangibles, which represent a pivotal breakthrough, and it occurs when an organization (painfully) develops core competencies and skills that allow it to outperform its competitors, especially for what concerns customized differentiation.

Intangibles constitute an ongoing challenge for accountants (Giuliani & Marasca, 2011; Roslender & Fincham, 2001) and their recording is a constant dispute, with problematic consequences even on market and performance valuation, exemplified by the increasing gap - softened during recessions – between market and book values, mostly attributable to relevant but not (adequately) accounted for intangibles. International homogeneous accounting treatment for intangibles is still a daunting target (Córcoles, 2010).

Intangible value is hidden in the balance sheet by inadequate accounting, but not in the profit & loss account or in the cash flow statement, where intangible capital incremental contribution to profit is detectable.

This paper starts with a comprehensive intangible valuation approach, with a consequent accounting analysis of operating leverage and scalability, linked to financial leverage and market value assessment by interacting parameters, consistent with a Modigliani & Miller optimal capital structure scenario. Intangibles, often underrepresented in the balance sheet, typically constitute a significant incremental EBITDA driver, which expresses the dominant income-driven cash flow source. Intangibles, which are the invisible "glue" behind going concern and value creation, not only enhance strategic differential value, but are also likelier to make results more sustainable in the future, so easing proper debt service.

DCF or EBITDA calculus is currently used even for the market valuation of intangibles; even if this fact is well known by academics and

practitioners, some further considerations, based on intangible driven cash generation, may add originality to the discussion of IC valuation and debt servicing. Asset-less incremental EBITDA, driven by intangibles, reinforces debt service capacity, through "economic" liquidity, originated in the income statement.

The paradoxical relationship between intangibles and debt (discouraged by lack of intangible collateral value but enhanced by its cash flow contribution to debt servicing) is critically examined, considering the impact of information asymmetries, traditionally embedded in intangibles, on debt rationing.

Innovative findings show that deeply rooted asset backed lending attitudes, deriving from an ancestral agricultural background where land and real estate incarnate value, are increasingly overcome by cash flow-based lending, driven by inventive business models and their income generating factors, more and more guided by intangible components and consistent with the knowledge economy framework.

Some practical tips, to soften outstanding issues are lastly enumerated, together with hints for future research avenues.

4. The difficulty to identify a fair value for patents according to IAS 38

IAS 38 (§ 12.) defines an intangible asset as "*an identifiable non-monetary asset without physical substance*". The definition requires an intangible asset to be identifiable to distinguish it from *goodwill*. An asset is identifiable if it either:

a) is separable, that is, is capable of being separated or divided from the entity and sold transferred, licensed, rented, or exchanged, either individually or together with a related contract, identifiable asset or liability, regardless of whether the entity intends to do so; or

b) arises from contractual or other legal rights, regardless of whether those rights are transferable or separable from the entity or from other rights and obligations.

Intangible assets may be carried at a re-valued amount (based on fair value) less any subsequent amortisation and impairment losses only if fair value can be determined by reference to an active market [§ 75.].

Such active markets are expected to be uncommon for intangible assets [§ 78.]. According to IFRS 13, Appendix A, an "active market" is "a market in which transactions for the asset or liability take place with sufficient frequency and volume to provide pricing information on an ongoing basis".

The classification of the main financial / market evaluation methods (see par. 6) is consistent with international accounting principles; according to IFRS 13:62, three widely used valuation techniques are:

- market approach – uses prices and other relevant information generated by market transactions involving identical or comparable (similar) assets, liabilities, or a group of assets and liabilities (e.g. a business)
- cost approach – reflects the amount that would be required currently to replace the service capacity of an asset (current replacement cost)
- income approach – converts future amounts (cash flows or income and expenses) to a single current (discounted) amount, reflecting current market expectations about those future amounts.

In some cases, a single valuation technique will be appropriate, whereas in others multiple valuation techniques will be appropriate [IFRS 13:63].

5. License or sale?

Intangible transactions may temporary or permanently transfer the property or the right to use the patent or trademark, being alternatively classified under a license or sale agreement. A patent can be used to protect or to earn licensing revenues (Ignat, 2016).

The perimeter of a license is proportional to the value of the patent.

Even if many comparability problems are similar in both circumstances, some major differences arise, and may be fiscally significant:

- (temporary) licenses are more common within the group, where information asymmetries are minimized, and synergies shared, and on an international basis, to bypass geographical exclusivity problems – and

so making arm's length comparisons applicable but more difficult to estimate;

- definitive sales may conversely occur even outside (international) groups, especially when a small and independent company, who owns a promising patent (or, less frequently, a still appealing but declining brand), is aware of the intrinsic and potential value of its intangible, but lacks the economic and financial soundness to properly exploit it, especially abroad;

- licensing may typically be riskier than selling for the owner of the intangible, since in many cases the royalty rate depends on unknown characteristics of the licensee (when the royalty is based on the licensee's output or sales, the rate may vary according to the turnover of the licensee);

- risk is asymmetrically transferred from the seller/licensor to the buyer/licensee, both in its dimension and timing, with a potentially not negligible impact on the tax base and its repartition in different fiscal years (the longer the period, the higher the possibility of smoothing incomes); albeit this parameter is difficult to estimate, it should be carefully investigated, together with its economic and fiscal impact; risk transmission is definitive in sales (unless there are earn-out or other conditional clauses), being otherwise shared and diluted across time in license agreements.

A combination between licenses and sales is always possible, especially when a license contract contains a put & call option, according to which after a certain time span and at a stated price, the intangible may be purchased by the licensee or sold by the licensor. This option has a deferred fiscal impact, which may be uneasy to assess and challenge, especially if the option structure is complex and depends on different contingent states of the world.

Legal ownership of the intangible is not exclusively linked to its exploitation, not only because of possible licensing, but also because of the versatility of the intangible, which can be exploited with partnership agreements, risk sharing, common investments, etc., within an articulated international value chain, where it may prove difficult to estimate the value of each segment.

• A license generally contains some or all the following financial provisions:

- Upfront payments;
- Ongoing pre-commercial payments;
- Patent cost reimbursement;
- Milestone payments;
- Annual minimum royalties;
- Research support;
- Sublicense income sharing;
- Manufacturing;
- Earned royalties or sales/profit sharing.

Most licenses include some form of upfront payment, variously called a license issue fee, a technology transfer fee, technology access fee (…).

The upfront payment reflects the value of the technology at the time is being transferred. For an embryonic academic technology that lacks both market and technology validation, this initial value will be relatively low, and so therefore will be the upfront fee.

For the academic institutions, a key element of the upfront value of the technology is the investment in legal fees that they have put into turning scientific data and publications into an intellectual property portfolio that can be licensed to a corporate partner. Academic institutions normally insist on recouping that investment upfront, in part so they can redeploy the funds into new inventions.

Newly formed start-up companies are usually cash poor. A wise licensor will typically not seek to suck much of that expensive cash out of the company in upfront payments but will want to see those funds go into developing the technology. Rather, the licensor will generally agree to be compensated in shares of the licensee, purchased at a nominal par value.

When a large company licenses technology from a smaller, early stage company, the agreement normally includes a purchase of equity in the smaller company by the large one.

From the licensor's perspective, the validation of their technology that the license demonstrates means that the company has reached a significant value-added milestone.

Most licenses include several "pre-commercial" payments, made while the technology is still under development and before it is generating product revenues for the licensee.

Milestone payments reflect the increase in the value of the technology to the licensee as the licensee makes progress in developing the technology.

Developmental milestone payments are particularly common with life sciences inventions.

Annual minimum royalties ("AMR") refer to payment that are paid in advance, at the start of the license year. AMR typically start low and escalate over time.

An AMR also serve as a due diligence mechanism. If the licensee has lost interest in the technology, either because it doesn't work or because the is no market interest, then the licensee will terminate the license and return the technology to the licensor rather than make an AMR payment.

When a technology is transferred at an early stage, the licensee frequently needs the licensor to help with the development of the technology.

Exclusive licenses always give the licensee the right to sublicense the technology to third parties. Non-exclusive licenses generally don't include such a right, because the licensor can still grant additional licenses to any interested third parties.

A "pass-through" is frequently found in licenses where the licensee is a large company. In such licenses, the payment obligations accepted by the licensee are equally binding on any sublicenses.

License agreement frequently include provisions for the licensor to manufacture product for the licensee. This is particularly likely to be true in the preliminary stages of the license when the bulk of the know-how and capabilities reside with the licensor and the licensee is still starting to ramp up their capabilities, but it may well extend on an on-going basis to provide for the licensor to manufacture product for commercial sale by the licensee.

Royalties on sales, also named to as “running royalties” and “earned royalties”, are payments made by the licensee once the licenses products have reached the market place. The licensor generally receives a percentage of the licensee’s sales of the licensed products, usually quarterly in arrears. Such post-commercialization payments generally provide the biggest economic return to the licensor from the license if the product is successful.

The royalty base is the measurement, normally in term of “Net Sales”, of the licensee’s sales of the licensed product on which the royalties will be paid.

There are two ways royalties are calculated:

1. A royalty based on the money value of the product’s sales; or

2. A royalty based on the units of product sold.

A royalty based on sales is expressed as a percentage of the monetary value of product sales.

Normally, the royalty rate should be higher at higher levels of sales, rather than decreasing as sales increase. The current year’s Annual Minimum Royalties will clearly be creditable against the earned royalties due.

In some cases, the parties may agree to split the profits from the sale of the licensed products rather than provide a royalty. Profit splits are often encountered in licenses by biotechnology companies of late stage products to pharmaceutical companies.

Profit sharing license agreements require a considerably more detailed set of financial provisions to identify shat costs are allowable so that the licensor will be able to audit the payments they eventually receive. Profit sharing arrangements work best if the licensee sells a relatively small number of products, so that cost allocations are clear and transparent. This is one reason why they work well in the pharmaceutical industry.

6. A Comprehensive Valuation Approach for Intangibles and Patents

Intangible assets, such as patents or trademarks, are particularly difficult to evaluate, due to their intrinsic “immaterial” nature and many

different - complementary – appraisal methods are traditionally used within the business community; valuation issues are even more complicated for non-tradable or not deposited intangibles, such as know-how, trade-secrets, goodwill, etc., characterized by limited if any marketability, higher and pervasive information asymmetries and less defined legal boundaries.

These difficulties in market evaluation are even more evident considering that, from an accounting point of view, according to IAS 38 there is no active market for intangibles, typically undetected, and it is consequently difficult to assess their fair value.

The distinction between different intangibles has, however, to consider their intrinsically versatile nature (due to their intangibility, with consequent little if any problems of transportation, storing, etc.) according to which they may be easily moved and frequently combined, looking for precious synergies (e.g., a branded product whose quality is enhanced by various patents). When a combination of intangibles is sold or licensed in a package-deal "bundled" transaction, often "embedded" in some material assets, specificity increases and then the fiscal detection of their value may become even more difficult, trespassing to arbitrariness.

Market valuations of intangibles, such as patents or trademarks, specifically address the peculiar appraisal problem [see Amram (2005); Cohen (2005); Duffy (2005); Hand & Lev (2003); Parchomowsky & Wagner (2004); Reilly & Schweihs (1999)] with *ad hoc* empirical or analytical methods; empirical methods are based on allegedly comparable market prices (hopefully referring to … "uncontrolled" transactions) and value is estimated upon guideline transactions of comparable assets, whereas analytical methods have a sounder scientific background and a longer appraisal tradition, mainly referring to financial and/or economic flows estimates, deriving from exploitation of the intangible.

Intangibles may be valued with many complementary methods (cost-based; income-based or market-based, as shown below), whose practical implications go well beyond plain appraisals, concerning also proper accounting or ability to promptly serve debt.

Issues relating to the valuation of intangibles are surfacing with unprecedented regularity and posit an intriguing challenge for the accounting fraternity that is entrenched in the traditional ascendancy of "reliability" over "relevance" (Singh, 2013).

Intangible assets, such as patents or trademarks (Salinas & Ambler, 2009), are particularly difficult to evaluate (Oestreicher, 2011; Moro Visconti, 2012), due to their intrinsic "immaterial" nature and many different - complementary – quantitative and qualitative evaluation methods (Lagrost *et al.*, 2010; Andriessen, 2004) are traditionally used within the business community; valuation issues are even more complicated for non-tradable or not deposited non-routine intangibles, such as know-how (Moro Visconti, 2013), trade-secrets and unpatented R&D (Ballester, Garcia-Ayuso & Livnat, 2003), goodwill, etc., characterized by limited if any marketability, higher and pervasive information asymmetries and less defined legal boundaries, especially within increasingly specific businesses.

Intangible assets may anyway hardly be estimated on a single basis, being mostly transacted within intangible package deals. These difficulties in market evaluation are even more evident considering that, from an accounting perspective, according to IAS 38 there is no active market for intangibles, typically undetected, and it is consequently difficult to assess their fair value.

A technology appraisal is a written analysis of its intended value, considering the methodology and data used (quoting the sources).

The main financial / market methods used for intangibles' fair pricing, with an appropriate rating and ranking, selectively applicable to intangible assets, are the following:

1. *cost-based methods*, with an estimate of the "what-if" costs to reproduce or replace intangibles from scratch, if there is some relationship between cost and value. This method ignores both maintenance and the opportunity cost of time (reproducing an intangible may take years, whereas its missed use is due to generate a lack of income) and is not very useful for income generating assets, such as performing patents or trademarks; cost to cost comparisons are difficult to imagine, especially if they are to be protracted over years; even if

intangibles strongly depend on long cumulated costs, their perspective value may hardly be inferred from past expenses and is also highly volatile and instable and cost differs from the value. To the extent that costs cannot typically be capitalized, their accounting track record may (partially) be detected from past income statement recordings.

2. *income methods*, based on the estimate of past and future economic benefits, assessing the ability of the intangible to produce licensing income (royalties, which etymologically derive from "sovereign rents") or sale of the intangible; they may include:

- capitalization of historic profits deriving from the exploitation of the intangible;
- Discounted Cash Flow (DCF), to estimate Net Present Value (NPV), duly incorporating risk factors in the discount rate, such as technology venture capital risk;
- gross profit differential methods; they look at the difference in sales price between an "intangible backed" product (branded, patented, with embedded know-how …) versus a generic one; the profit differential is then forecast and discounted;
- excess or premium profit methods; like the gross profit, it is determined by capitalising the additional profits generated by the business over and above those generated by similar businesses, which do not have access to the intangible asset. Excess profits can be calculated by reference to a margin differential;
- relief from royalty method: based on the assumption that the owner of the intangible is "relieved" from paying a royalty to obtain its use, the process considers the hypothetic "what if" royalty that a potential user would be willing to pay and discounts its projection; a comparable market range of "reasonable" royalties may derive from careful arm's length benchmarking.

3. market-based methods, evaluating an intangible asset by comparing it with sales of comparable / similar assets (considering their nature; using functional analysis …). Information asymmetries often conceal the real (mostly secret) nature of the allegedly comparable transaction. A market-based variety may refer to the evaluation of the incremental equity, with indicators of the business surplus, given for example by the Tobin Q (Tobin, 1969), the ratio between the market value and

replacement value of the same asset; a market value exceeding the replacement value may be a numerical consequence of valuable intangibles.

The purpose of the evaluation may change according to the context and the foreseen scenario, and may be targeted at the following different values:

- Fair Market Value - The price, expressed in terms of cash equivalents, at which property would change hands between a hypothetical willing and able buyer and a hypothetical willing and able seller, acting at arm's length in an open and unrestricted market, when neither is under compulsion to buy or sell and when both have reasonable knowledge of the relevant facts (The International Glossary of Business Valuation Standards);
- Investment Value - The value the intangible would be worth, considering the specific buyer's intended use (and so with use-value higher than exchange-value);
- Intrinsic Value - The value that an investor considers, based on an evaluation of available facts, to be the "true" or "real" value that will become the market value when other investors reach the same conclusion (Pratt, 2003, p. 75).
- Liquidation Value – The company may pass from a going concern to a break up context, this being a particularly conservative scenario for intangibles, especially if not autonomously tradable.

While income and market-based methods may theoretically seem based on accrual or, respectively, cash flow accounting, they tend to share common parameters, softening the Manichean difference between these two apparently antithetical accounting procedures. A synthesis of economic (based on accrual accounting of revenues and costs) and financial flows, is represented by their (only) common parameter – EBITDA - as it is shown in figure 1.

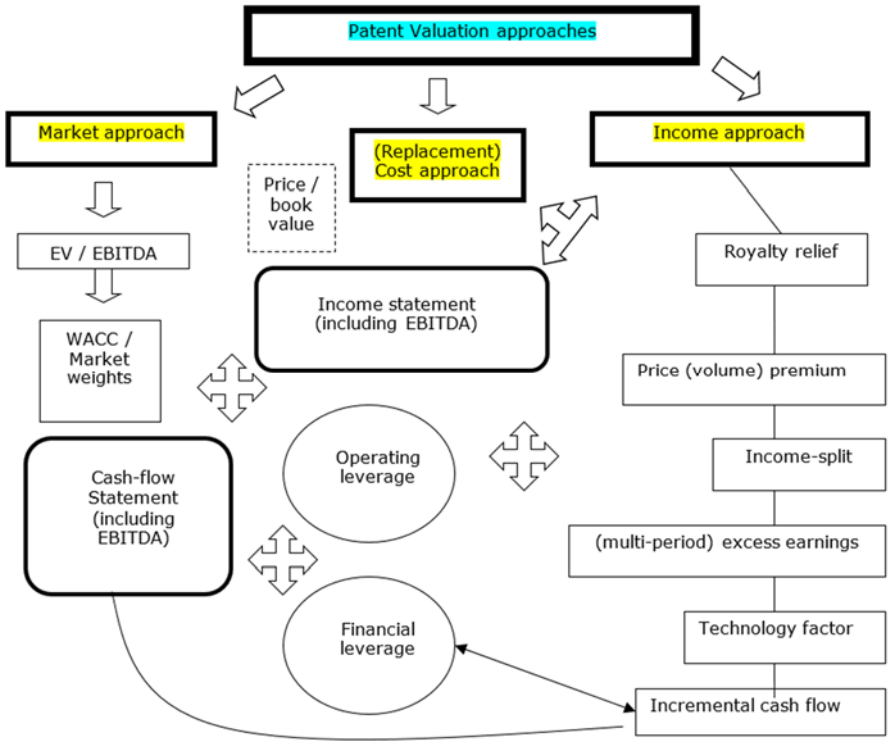


Figure 1 – *Patent Valuation methodologies*

Factors affecting the value of a patent include:

- Strength/weakness of the patent (how easily are they avoided or engineered round);
- Characteristics of the patent (what the patent protect);
- Other technology rights included.

- Market and income valuations need to consider patent risk factors like the following:
- R&D risk (the risk that the technology cannot be successfully developed into a functional product);
- FDA risk (the risk that the product won't be found safe and effective);
- Standards risk (the risk that a standard setting body will adopt a standard that is incompatible with the product);

- Manufacturability risk (the risk that the product can't be manufactured at an acceptable cost);
- Marketing risk (the risk that the marketing launch of the product is unsuccessful);
- Competitive risk (the risk that a competitor using a different technical approach solves the same problem and reaches the market first);
- Legal risk (the risk that a competitor receives a patent that block others from entering the market and isn't willing to grant a license).

Valuation methodologies change over time and depend on the quality of information that typically increases over time in quantity and depth.

6.1. Cost-based methods

The cost approach seeks to measure the future benefits of patent ownership by quantifying the amount of money that would be required to replace the future service capability of the subject property. The starting point in this method is either the cost of reproduction of the property or its replacement cost.

The cost approach is rarely useful in the valuation of early-stage technology : the cost of developing technology is seldom relevant to its value.

A cost-based valuation is divorced from the value of the technology.

The concept of using sunk cost to value a technology is that the developer wants to first recoup their investment in developing the technology and then secure a return on that investment.

The problem with this approach is the fundamental philosophical question of whether the cost to develop a technology is relevant to its on-going value.

Academic institutions always seek to recoup the discretionary investment they have made in securing patent rights in the license agreement. Such costs are identified separately from any other up-front cost and may be substantial if the technology has been under development for an extended period.

In licensing copyright-protected software developed in an academic setting, recouping the sunk cost may be infeasible. A company interested

in using the software could instead simply hire the researcher who wrote the code and get them to recreate it.

In corporate licensing transactions, where the licensor has made a substantial investment in developing the technology, they will want to ensure that they recoup that investment in upfront and milestone payment.

6.2 Market valuations

The market approach measures the present value of future benefits by obtaining a consensus of what others in the marketplace have judged it to be. There are two requisites: (1) an active, public market, and (2) an exchange of comparable properties. Start up technology rarely meets these valuation requisites.

Patents without established market values (e. g., no negotiated royalty rates) are often valued by comparing the number of citations the patent has received to the numbers received by other patents whose market values are established. For recently-issued patents, which have not had time to accumulate citations, this procedure can be noisy or even inapplicable (Falk and Train, 2016).

Market valuations may use as preferential methods either DCF or directly an EBITDA multiplier, inspired by (intrinsically uneasy) comparisons of intangibles. DCF theoretically stands out as the optimal method, being inspired by the golden rule according to which “cash is king”.

DCF is ubiquitous in financial valuation and constitutes the cornerstone of contemporary valuation theory (Singh, 2013). The robustness of the model as well as its compatibility with the conventional two-dimensional risk-return structure of investment appraisal makes it suited to a multitude of asset/liability valuations. Accounting standards across the globe recognize the efficacy of this model and advocate its use, wherever practicable. FAS 141 and 142 of the United States and IAS 39 that relate to the accounting of intangible assets, also recommend the use of DCF methodology for imputing a value to such assets.

Market evaluations also frequently use a standardized EBITDA multiplied over time (from 2/3 up to 15 or more times/years, in exceptional cases such as patented killer application or “superstar”

brands) and this (apparently) simple multiplication brings to an Enterprise Value (EV), attributable to debt-holders and, residually, to equity-holders. This approach is consistent with the accounting nature of EBITDA, which is calculated before debt servicing.

EV / EBITDA multipliers may be connected to price / book value or Tobin q parameters, which reflect the differential value of intangibles under a hypothetical cost reproduction hypothesis, so representing a precious bridge between otherwise disconnected market and cost appraisal methods.

As a rough calculation, the EV multiple serves as a proxy for how long it would take for a complete acquisition of the entire company (including its debt) to earn enough to pay off its costs (assuming no change in EBITDA and a constant added value contribution from the IC portfolio). Temporal mismatches between the numerator and the denominator may bias the ratio and should accordingly be minimized.

Equity and debt value may be jointly inferred from an EBITDA multiplier, which estimates EV, and, after deduction of market value of debt, residual market value of equity. Whenever residual market value of equity exceeds its book value, BV, (price > book value; P/BV> 1), an implicit safety net for principal debt repayment emerges. Being EV a surrogate for market capitalization (price), its relationship with market-to-book and Tobin q, driven by the presence of intangibles (Valladares Soler & Cuello de Oro, 2007; Chen, Cheng & Hwang, 2005) seems even more evident.

The stream of (hopefully) growing and not ephemeral Operating Cash Flows - CFo - (marginally attributable to the intangible strategic contribution to the overall value) incorporates growth factors (Tan *et al.*, 2007), whereas the weighted average cost of capital (WACC) discounting denominator embodies market risk elements, as recognised by debt and equity underwriters. Moreover, cash flows are a cornerstone of debt service, as it will be shown later. Qualitative issues, such as consistency, durability, depth of coverage, etc., concerning IC, may strategically impact on future EBITDA, cash flows and consequent value. WACC may also be affected by the asset substitution problem and inherent wealth transfer from debt- to equity- holders (or vice-versa), as it will be shown in the next paragraphs.

What matters, should the valuation consider only IC marginal contribution to the overall company's value, is just described by differential/incremental CFo or EBITDA, made possible by IC strategic contribution, which is, however, often uneasy to isolate. Residual incremental value, not attributable to specific IC components is allocated within the goodwill cauldron.

Being CFo derived from EBITDA, as depicted in figure 3, the link between key market methods (possibly complementary, rather than alternative) is evident. This is a significant, albeit trivial, finding, somewhat misperceived by the current literature, with an important impact on IC valuation. Figure 3 shows the functional links existing at the level of the profit and loss, balance sheet and cash flow statement.

Calculation of expected benefits with Net Present Value (NPV) is given by the following formula, considering NPV accruing to equity-holders:

$$NPV_{equity} = \sum_{t=1}^{n} \frac{CFN_t}{(1+K_e)^t} - CF_0$$

where:

CFN = Net Cash Flow; t = time; K_e = Cost of equity; CF_o= initial investment

- NPV is (also) used in the cost method

Proper calculation of NPV should include even the other factors, incorporating in Net Cash Flows geographic limitations, restrictions, exclusivity, etc. One well known critical problem with NPV calculation is represented by the intrinsic difficulty to properly estimate cash flows, especially in the presence of unforeseeable events or flexibility options, particularly frequent with patents. A patent is like a real option, because it allows its owner to choose between exclusively commercializing the patented invention sometime during the patent term or foregoing commercialization altogether. See Cotropia (2009).

As Silberztein (2011), points out "There is currently no international consensus on the circumstances where financial valuation approaches and the Discounted Cash Flow (''DCF'') may be appropriate for applying the arm's length principle", and again: "one of the main difficulties

regarding the application of these methods is that they are based on inherently uncertain projections" (See TPG, Chapter VI, C.4 Arm's length pricing when valuation is highly uncertain at the time of the transaction).

6.2.1 Comparability factors

Patents are difficult to compare, because there are intrinsically "unique" (if an invention is not unique, it cannot be patented!); relevant patentability requirements include novelty and non-obviousness.

Significance of market comparisons is indirectly proportional to the intrinsic value of patents; this brings to a paradoxical situation where originality and uniqueness are a core distinctive value of patents, with a consequent positive impact on its potential fiscal value, but at the same time represent a major obstacle to its fair tax assessment. The more a patent is specific and worthy, the less it is detectable.

Possible comparability factors for patents include:

- the expected benefits from the intangible property (possibly determined through a net present value calculation).
- any limitations on the geographic area in which rights may be exercised;
- export restrictions on goods produced by any rights transferred;
- the exclusive or non-exclusive character of any rights transferred;
- the capital investment (to construct new plants or to buy special machines), the start-up expenses and the development work required in the market;
- the possibility of sub-licensing,
- the licensee's distribution network,
- whether the licensee has the right to participate in further developments of the property by the licensor.

The market price, depending on comparability factors, may be difficult to find, especially if the intangible is unique. This is the case especially for patents that are affected by a paradox: the more they are exclusive, the higher their value – but also the lower their comparability…

Market information may derive from composite sources as:

- internal (confidential) database

- published surveys and researches that may establish norm standards within an industry;
- public announcements of deals (of listed companies, etc.) and public databases
- details from litigation and required disclosure of license terms
- state of the art
- word of mouth.

Deal databases may derive from the following sources (for fee):

- RoyaltySource (www.royaltysource.com);
- TechAgreements (www.techagreement.com);
- RoyaltyStat (www.royaltystat.com);
- Business Valuation Resources (www.bvresources.com);
- Recap by Deloitte (www.recap.com);
- PharmaDeals (www.pharmadeals.net);
- Windhover (www.elsevierbi.com/deals).

6.3 Income approach

The income approach focuses on the income-producing capability of the patents. The value is measured by the present worth of the net economic benefit to be received over the useful life of the patent.

The amount and the pattern of the income stream is evaluated with its duration and with the risk associated with the effective realization of the predicted income (see figure 1).

The income approach must properly consider the forecast profit and losses deriving from the patent.

The key differences between the classical high discount rate NPV approach and the Risk Adjusted NPV approach is that in the latter risk is accounted for explicitly, and the discount rate used is a “cost of money” discount rate, not a risk-based discount rate.

An NPV-based valuation has the benefit that it considers trades off near term and long term financial terms appropriately.

Limitations of the NPV-based valuation are the following:

- quality depends critically on the quality of the data;
- critical data may not be available for technologies at a very early stage;

- susceptible to "garbage in – garbage out" issue.

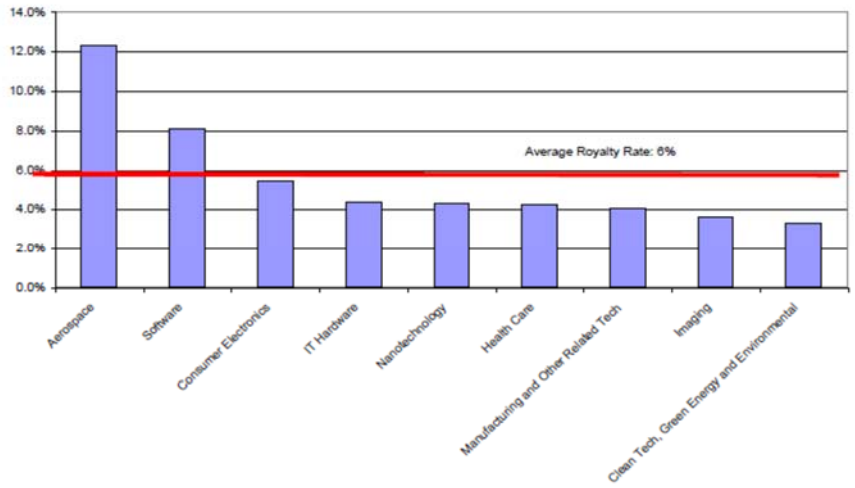
Monte Carlo methods are another approach to accounting for risk.

Both the NPV and raNPV approaches require the analyst to make assumptions about all the parameters of the project – its costs, its revenues, the probability of success for each phase in the raNPV approach (...) – and then generate a single number that represents the analyst's best estimate of the present value of the project.

Monte Carlo methods, by contrast, allow the analyst to put ranges round the various parameters, allowing, for cost over-runs in development and for the possibility, that sales may be either higher of lower than expected. The NPV is then calculated for each combination of the estimated parameters, and the results are presented as a distribution of the probability of the NPV.

Monte Carlo gives much more sophisticated analysis of risk than NPV or raNPV approaches but has the limitations that data unlikely to be available for early stage academic technologies.

Figure 2 - *Average Royalty Rate by Major Technology Types*



According to Degnan and Horton (1997), valuation methodologies are the following:

Valuation Methodology	In-Licensing	Out-Licensing
Discounted Cash Flow	56%	49%
Profit Sharing Analysis	52%	54%
Return on Assets	38%	27%
25% Rule as a Starting Point	24%	30%
Capital Asset Pricing Model	11%	10%
Excess Return Analysis	8%	7%

Table 1 - *Relationship of Royalty Rate to Magnitude of Improvement*

Median Royalty Rates	Pharma	Non-Pharma
Revolutionary	10-15%	5-10%
Major Improvement	5-10%	3-7%
Minor Improvement	2-5%	1-3%

EBITDA is also indirectly reflected in (at least some) income valuation methods, for example, those concerning royalty relief differentials or marginal economic surpluses made possible by IC exploitation, and so it constitutes a significant and precious connection between market and economic methods. The (replacement) cost approach is apparently not so easily linked to EBITDA, even if the projection of reconstruction costs of the IC portfolio considers operating economic costs that are a core, albeit not exclusive, part of EBITDA. Revenues are missing in the replacement cost method whereas key costs described for example by depreciation are not present in the EBITDA.

Being the cost method deeply linked to accrual accounting, it may suffer from somewhat misleading historical cost convention procedures, which traditionally underestimate IC accounting and their potential contribution to value creation. Accrual accounting represents an obstacle for the appraisal of the IC contribution to CFo creation, even if the links pivoting around EBITDA may soften these inconveniences (Boujelben & Fedhila, 2011, p. 481).

EBITDA is sometimes used as a proxy for CFo, representing a kind of price to cash flow multiple, unaffected by leverage and depreciation

policies. This proxy is however misleading, since CF_0 is derived from EBITDA, considering also Capital Expenditure (Capex) and Net Working Capital variations; while fixed asset investments and their cashless depreciation may hardly be affected by IC, typically not capitalized, accounts payable included in NWC often reflect operating debt connected to costs (for R&D, advertising …) associated with IC.

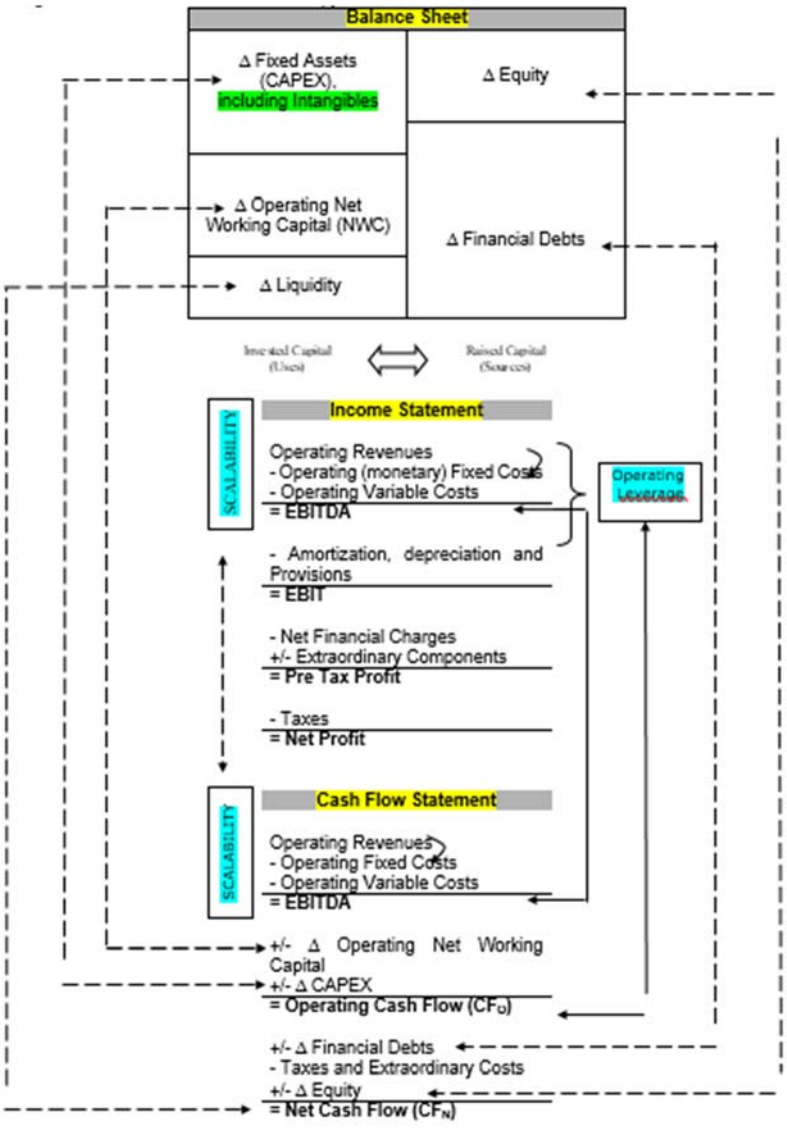
EBITDA is also a key parameter for assessing debt service capacity, so being linked even to classic capital structure concerns. To the extent that debt is properly served with positive cash inflows deriving (also) from EBITDA (and then CF0, as depicted in Figure 3), a key relationship can consequently be established between market / income valuation models and bankability concerns.

Capacity to serve debt is often measured by EBITDA multipliers over negative interests (and by cover ratios, described in the appendix); being EBITDA a differential and incremental economic / financial flow from operations, it should conveniently exceed negative interests at least 4-5 times, considering also its contribution to the coverage of other monetary costs, such as for example taxes.

Being IC appraisal so difficult and slippery, synergistic combination of different complementary techniques is, whenever possible, highly recommended. Traditional financial statements do not provide the relevant information for managers or investors to understand how their resources – many of which are intangible – create value in the future. IC statements are designed to bridge this gap by providing innovative information about how intangible resources create future value. Published IC statements are, however rare documents (Mouritsen, Bukh & Marr, 2004).

Valuation approaches may be synergistically linked to operating and financial leverage, since they contain key accounting and economic/financial parameters, as it will be shown in the next paragraphs. A synthesis of intangible appraisal methods, which may be summarized in a comprehensive valuation dashboard, is depicted in Figure 1. Figure 3 shows the accounting interaction of balance sheet, income statement and cash flow statement.

Figure 3 – *Interaction of balance sheet, profit and loss account and cash flow statement*



These evaluation methods may well be linked to the Modigliani & Miller, 1958 (M&M) theorems about optimal capital structure, which will be examined afterwards, and to the key parameters embedded in their formulation:

- Market approach is proxied by M&M proposition I and related cost of capital;
- Replacement cost is based on cumulated reconstruction costs and is also linked to lost opportunities, whose estimate may somewhat refer to differential cumulated EBITDAs and other economic / financial parameters, embedded in M&M formulations;
- Income approach relies on EBIT / EBITDA differential contribution to value.

Coherently with IAS 38 prescriptions, DCF is the key parameter for both accounting and appraisal estimates, so representing the unifying common denominator of cost, income or market-based methods, which regularly need to find out their cash part. Cash is also directly linked to debt service capacity, so connecting intangible value creation and its book value or market appraisal with its financial coverage, always remembering that “cash is king”.

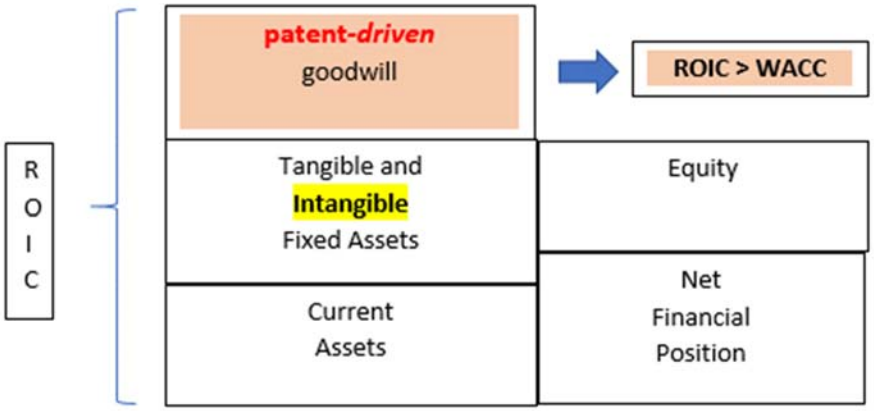
6.4 Competitive Advantage and Patent-driven goodwill

Competitive Advantage Period (CAP) is the time during which a company is expected to generate returns on invested capital (ROIC) from incremental investments (in R&D, patents, etc.) that exceed its weigthed average cost of capital (WACC).

The added value incorporated in CAP is given by strategic drivers that are resource-based and that may be related to the patent exploitation.

Extra returns may so be patent-driven, and CAP is a proxy for goodwill, as shown in Figure 4.

Figure 4 - *Goodwill as a positive differential between return and cost of invested capital*



CAP can be linked to Economic Value Added (EVA) that is cumulated into Market Value Added (MVA). EVA is the difference between the return and the cost of invested capital, multiplied by the invested capital:

EVA = (ROIC – WACC)* Invested Capital (= Raised Capital = Equity + Net Financial Position)

ROIC and Invested Capital are adjusted to consider equity equivalents, as a proxy of market weights.

MVA is given by the difference between the patent-driven market value of the company and its invested capital, which corresponds to the present value of all the future EVA:

MVA = market value – invested capital = Present Value of future EVA = EVA_1 / (WACC-g)

Patent-driven CAP, EVA and MVA is given by excess returns compared to a market benchmark that produce economic rents over a time horizon that depends on many variables (expiration of the patent portfolio; ability to outperform the market, etc.).

6.5 Real Options

«A fairly robust economics literature exists which analogizes patents to real options. Real options create the right, but not the obligation, to purchase the underlying asset at a defined exercise price. A patent is like a real option, economists say, because it allows its owner to choose between exclusively commercializing the patented invention sometime during the patent term or foregoing commercialization altogether. Economists have taken this analogy and used real options analysis to place specific values on patents » (Cotropia, 2009).

When investments or assets, like patents, are evalued through NPV techniques, real options can be used to make forecasts more flexible (see Iazolino and Migliano, 2015).A real option is the right - but not the obligation - to undertake certain business initiatives, such as deferring, abandoning, expanding, staging, or contracting a capital investment project. Real options describe the key tensions that managers face between commitment versus flexibility or between competition and cooperation (Trigeorgis and Reur, 2017).

6.6 Quick and dirt valuation techniques

It is wise to express royalty rates in terms of Net Sales, not Net Profits. The most venerable rule of thumb in licensing is the 25% rule. According to this rule, the licensor should receive 25% and the Licensee should receive 75% of the pre-tax profit form a licensed product.

In the famous Uniloc cause, the Court underlined that "*the 25% rule of thumb is a fundamentally flawed tool for determining a baseline royalty rate in a hypothetical negotiation*".

The rule of 25% appears broadly applicable – if a company is seeking a license to a technology it must be because they believe they will derive some business benefit, either increased sales or decreased costs (see Azzone & Manzini, 2008).

The main limitations of the rule are the following:

- The 25% must be apportioned over all the technologies the licensee will need to develop for a finished product;
- The licensee may resist giving 25% of their net profits if they have to make a massive investment to develop and market a product.

7. Forecasting Patent Outcomes with Big Data and Stochastic Estimates

Prediction of future outcomes is particularly difficult. And when patents are concerned, uncertainties tend to grow, making valuation estimates hard. Imprecise forecasts bring to huge differences between expectations and real outcomes, i.e. to higher risk.

Both big data and stochastic estimates, especially if jointly considered, can soften these criticalities.

Characteristics as volume, velocity, variety, and veracity make big data particularly interesting for sophisticated economic and financial planning, where several variables stored in interoperable databases need to be simultaneously considered. Big data is driving better decision making and can help to detect growth drivers. Stochastic modeling is a form of financial modeling that includes random variables to estimate how probable outcomes are within a forecast to predict different states of the world (Moro Visconti, Montesi and Papiro, 2018).

8. A Synergistic Valuation of a Portfolio of Intangibles

Patents are often considered as a stand-alone asset and in that case, they suffer from isolation that can decrease their intrinsic value. Inventive and patentability efforts are time and resource consuming but can be hardly rewarding in many cases. Two strategic pitfalls that depress the patent potential value are attributable to:

1. Lack of economic-financial focus: inventors are concentrated on the technical aspects of their "creature" and often tend to underestimate the economic and financial aspects concerned with the patent exploitation. A patent needs to be technology-focused but also market-oriented;
2. Limited synergies with other intangibles. Inventions are seldom path-breaking and normally they are incremental, improving the state of the art. Inventions need to be continuously upgraded and linked to an intangible eco-system where they participate to synergistic value co-creation.

The valuation of patents is often assessed with respect to complemental IP strategies such as trademarks, design patents and utility models. A patent and trademark pair constitute a signalling device of the high expected value of the underlying invention from a

commercial point of view. (Thoma, 2015). Bundled intangibles are more difficult to copy and they increase entry barriers.

The distinction between different intangibles must consider their intrinsically versatile nature (due to their intangibility, with consequent little if any problems of transportation, storing, etc.) according to which they may be easily moved and frequently combined, looking for precious synergies (e.g., a branded product whose quality is enhanced by various patents) and creating the potential for fruitful tax planning. When a combination of intangibles is sold or licensed in a "bundle" transaction, often "embedded" in some material assets, specificity sours and then the fiscal detection of their value may become even more difficult, trespassing to arbitrariness.

Characteristics of intangibles are also difficult to isolate, and may overlap: "in some cases patents, because of their outstanding quality, may also have a very strong marketing effect like that of a pure trademark".

9. Scalable Patents, from Operating to Financial Leverage

Intangibles represent a flexible and resilient key part of competitive advantage, incorporating value-enhancing productivity and representing a fundamental constituent of cash flow production, so making debt servicing sustainable, as it will be shown even in the next paragraphs.

Operating leverage is a measure of how revenue growth translates into growth (Δ Sales) in operating income (ΔEBIT), a key economic margin which incorporates most of the economic and accounting impact concerning intangibles. It is a measure of how risky (volatile) a company's operating income is:

$$\text{Operating} \quad -\text{Leverage} \quad = \frac{\Delta \text{EBIT}}{\Delta \text{SALES}} = \frac{\Delta(EBITDA \ + Depreciati \ on / \ provisions \ )}{\Delta SALES} \quad (1)$$

The factors that influence operating revenues are:

- revenue volumes and margins, influenced by intangible items;
- variable costs;
- fixed costs, mitigated by intangible-driven productivity gains, which may strongly contribute pulling down the economic break-even point.

Operating risk may be reduced and better monitored with synergistic use of intangibles (intangibles are likely to have a positive impact on operating leverage, reducing fixed costs; protecting revenues; enhancing marginality ...).

Scalability is, broadly speaking, the ability of a business model to generate incremental demand (additional revenues) economically, i.e. without significantly increasing costs. In the presence of a scalable business, the operating leverage works as a multiplier of the EBIT.

Since any change in operating leverage affects a key parameter such as the EBITDA, it also has a financial effect, due to the circumstance that EBITDA is both an economic and financial margin, being represented by the difference between monetary operating revenues and costs, as it has been shown in figure 2. This well-known property has important side effects and is a key factor to understand why and to what extent financial and operating risk can be associated.

Since operating leverage indicates the translation of revenue changes on EBIT, which may be decomposed into EBITDA + depreciation/amortization, the differential impact of intangibles on EBIT may also be accordingly split: an economic / financial impact on EBITDA and an economic/asset (balance sheet) impact on cashless depreciation and amortization, which are in turn linked to cash flow sensitive Capex and, eventually, to operating cash flow. Any change in the economic marginality, affecting EBITDA and EBIT, so has an impact on operating cash flow, a key parameter to assess the financial soundness of the company and its ability to properly serve the debt burden. Operating cash flow, as it is shown in the appendix, is in turn associated with key financial parameters like cover ratio, NPV, IRR, WACC ... Interactions of key parameters may bring to significant insights; for example, if $IRR_{investment}$ > WACC, the return on invested capital exceeds the cost of raised capital, bringing to a positive NPV, with safety resources for debt service and residual incremental value for equity-holders.

10. Leverage and the Paradox of Intangibles: More Guarantees with Less Collateral?

Financial leverage, represented by the debt to equity ratio, paradoxically interacts with intangibles, since their presence in the asset's portfolio typically decreases residual collateral value, so

discouraging debt, whereas unique intangible assets are, on the other side, a fundamental pant of cash generating value, so representing a key factor for debt servicing.

Intangibles and their liabilities (García-Parra *et al.,* 2009). may so decrease leverage, even because tangible equity (i.e. book equity, net of intangibles) is often used in the denominator of the leverage formula, but their presence increases the ability to repay debt, and credit ratings are improved by innovation (Al-Najjar & Elgammal, 2013).

This paradox may be softened with a fair communication of the company's perspectives, so relevant for a proper debt servicing, underlying the key strategic role of intangibles. It may also be noted that tangible assets are increasingly worthless in a standalone context, their value strongly depending on a continuous interaction with intangibles, like software with hardware.

The circumstance according to which, in an extreme "intangible" context, typical of venture backed start-ups (whose main asset is represented by ideas with strong but uncertain potential for growth), debt is difficult to enforce, and so almost nonexistent, is a symptom of a strong relationship between physical marketable assets and borrowing capacity. In the valuation of intangibles, there is so a remarkable difference between going concern and break-up value, especially in the presence of tailor made and not autonomously tradable assets.

The value of the firm, in an ideal world with complete and perfect capital markets, is unaffected by the way the firm is financed - and so capital structure, in terms of debt to equity ratio, is in principle irrelevant (Modigliani & Miller, 1958). Being raised capital (equity + financial debt) the balancing counterpart of invested capital (net working capital + fixed assets, including intangibles), the financing mix also depends on the assets' composition. Whenever this composition is changed, and the firm invests in assets, such as intangibles, that are potentially riskier than those that the debt-holders expected, an asset substitution problem arises.

The value of an unlevered firm equals that of a levered firm, being debt irrelevant, and the market value of a firm (V) depends on its ability to generate operating cash flows (CFo), to be discounted using a consistent parameter such as the weighted average cost of capital

(WACC). The formula shows a strong accounting link between operating and financial leverage, particularly evident decomposing the numerator and considering the presence of the debt-to-equity ratio ($D_f/[D_f+E]$) as a weighting part of the cost of debt k_d, net of the fiscal impact (1-t), in the denominator, where also cost of equity k_e is present:

$$V = \sum \frac{CF_O}{(1+WACC)} = \sum \frac{(EBITDA \pm \Delta NWC \pm \Delta Capex)}{k_e \frac{E}{D_f + E} + k_d (1-t) \frac{D_f}{D_f + E}} \quad (2)$$

CFo may be split in its traditional composing entities: EBITDA, variation in Operating Net Working Capital (ΔNWC) and in capital expenditure (ΔCapex).

Leverage does not affect unlevered CFo, and WACC is theoretically unaffected, to the extent that any change in the cost of debt (rising with leverage, due to agency costs) is counterbalanced, in an ideal world, by symmetric changes in the cost of equity.

In synthesis, due to a kind of self-balancing effect, any leverage (Df/E) change affects weighting factors of WACC but it should not (optimally) modify it, nor should it affect the parameters in the numerator (EBITDA, NWC, Capex).

Financial leverage does not affect the numerator (being CFo accounted for before debt servicing), whereas also the WACC in the denominator is unaffected by debt to equity changes, where risk is shifted from shareholders to debt-holders when leverage grows, resulting in a zero-sum game balancing effect, again (only) in an ideal frictionless world.

As shown in figure 2, CFo (whose impact on IC is described in Boujelben & Fedhila, 2011), derives from EBITDA, which is simultaneously an economic and a financial margin (flow), representing a key link between Income and the Cash Flow statements; EBITDA is also strictly linked to EBIT, which is the target component of operating leverage, sensitive to operating revenue changes.

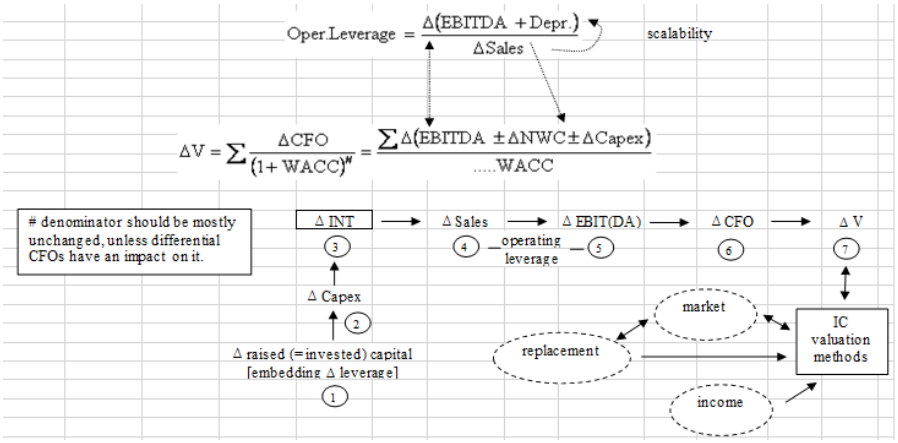
Debt capacity is a direct function of the assets' composition and its intrinsic riskiness, but assets must be considered, rather than stand-alone items, a synergistic bundle of tangible and intangible components, consistently with the *Coasian* theory of the firm and so incarnated by an integrated nexus of contracts, where know-how and goodwill represent the invisible glue behind intangible driven value, which represents a kind of knowledge-based equity (Maditinos *et al.*, 2011).

In the presence of intangible investments, lending should conveniently pass from an asset-based to a cash flow-based approach, where liquidity contribution is worth more than (tangible) asset-backed leverage. Even if the breakup value of intangibles may be negligible, especially if they may not be autonomously traded, the probability to depart from a going concern scenario may be less likely in the presence of a good intangible portfolio. Asset substitution (from safer to riskier asset composition) may so, in practice, misrepresent the company's solidity, exaggerating its risk profile. Intangibles, in pills, are linked to weaker if any guarantees, within a less likely scenario of enforcing them. IC unspecific value, ontologically unfit to be used as "material" collateral, yet has positive debt service implications, through its cash generating capacity.

Intangible investments do not necessarily absorb more debt, whereas they can ignite productivity gains (roughly measured by EBITDA increases), consequently easing bankability.

The value chain that links leverage to intangibles is represented in Figure 4, which contains a dynamic flow chart, starting from leverage and raised capital, to be invested in fixed assets (Capex), such as intangibles, which boost sales and then, consequentially, incremental EBITDA and operating cash flows, ultimately increasing differential value, linked to IC valuation methods and, through operating value, to intangible driven scalability.

Figure 5 - *The Leverage – Intangibles Value Chain*



11. Information asymmetries and Debt Rationing

Information asymmetries have a paradoxical impact on intangibles, since, in many cases they are needed and looked for, deterring imitation, as it happens with know-how and, to a lesser extent, with patents, whereas in other cases they cause communication problems that may damage brands and the external perception of the corporate image. Information asymmetries are so intrinsically embedded in intangible items, whose value is uneasy to account for and disclose (Arvidsson, 2011; Singh & Kansal, 2011; Kristandl & Bontis, 2007). The prudential exclusion of home-grown intangibles from the balance sheet increases information asymmetries, hampering comparability.

Appraisal and diffusion of the company's market value, with reference to its somewhat mysterious intangible component, may so be misrepresented, causing market failures and misbehavior, in the form of adverse selection, moral hazard or other corporate governance criticalities.

Since intangible assets are intrinsically difficult to estimate, their value may be misperceived and downgraded, with market failures that typically interest investors, in the form of (potential) debt-holders or shareholders, which may be frightened or discouraged.

Debt capacity grows in the presence of tangible assets with potential collateral value given by applicable guarantees, as confirmed by the seminal paper of Jensen & Meckling (1976), whose theory of the firm is based on agency problems created by the coexistence of debt and outside equity with inside penniless managers.

Intangibles intrinsically incorporate information asymmetries (Leland & Pyle, 1977; Aboody & Lev, 2000) and inside managers command superior information over the firm's value and prospects, if compared to outsiders; information asymmetries bring to sub-optimal decisions and may prevent capital or debt collection, so causing debt rationing problems which may block financing of valuable – and IC sensitive - projects.

Corporate governance failures and conflicting interests among different stakeholders (from conspiratorial IC managers to … sometimes gullible lenders) are also exacerbated by problematic debt monitoring and control rights in the presence of undetectable intangibles. Legal protection of debt-holders, including the right to grab collateral assets, and the (theoretical) right to liquidate the business, are weakened by the presence of intangibles with little if any alternative use.

Due to its slippery boundaries and immaterial plasticity, hardly observable and hazy intangibles are intrinsically noisy, and their differential impact on economic and financial flows is difficult to estimate and distinguish, as well as their potential replacement cost.

Noisy and cloudy investments in intangibles, typically stir up the asset substitution problems, to the extent that companies may exchange their negligible risk assets for riskier investments; since debt-holders typically have a fixed compensation, the higher risk put on assets is not typically compensated by higher rewards, and consequently there is a risk transfer from shareholders to debt-holders.

All these well-known corporate governance problems must be properly managed, aligning the interests of inside agents with those of external principals, with positive and value enhancing side effects, such as monitoring and accountability.

IC sharing among different firms is an intermediate solution between internal protection and sale (or, to a milder degree, licensing).

To the extent that information asymmetries and secrecy voluntarily soften with intangibles and knowledge sharing, economically stimulated by increasingly synergistic value chains (as the one represented in Figure 3), inappropriate behaviours (e.g., of counterfeiter competitors) may accordingly intensify and strategic differential value may be threatened. Progressive evolution from the industrial to the information age subverts traditional value chains, with an impact even on conventional lending, with a shift from asset-backed tangible collateral to hardly marketable but value enhancing intangibles.

The paradox of (elsewhere much appreciated) comparability is that, in many cases it represents a symptom of weak value, especially if concerning brands or patents, whose uniqueness (and consequent incomparability) is possibly the strongest fundament of intrinsic value. It may so be affirmed that value-destroying information asymmetries are, for certain contradictory features, a positive source of value; whereas these two distinct aspects represent a zero-sum game, approaching Pareto optimality, remains however a complex issue, uneasy to be generalized. More interdisciplinary research is needed even for this not trivial aspect.

Imitation of unprotected intangibles, intrinsically reduces information asymmetries, again with a controversial impact on value, producing trickle down and spill-over externalities but also destroying monopolistic secrecy and, with it, egoistic reward for innovative efforts, up to the point of discouraging R&D. Legal infringements are increasingly likely in a technological environment where information is easier to … copy and paste, storing and transferring it in real time, up to the point of making it publicly available through the libertarian Web.

Some mitigation strategies may soften information asymmetries:

- since the presence of intangibles increases the company's payoff upside potential, residually attributable only to equity-holders; issue of convertible debt may soften this risk / return asymmetry (Smith & Warner, 1979);
- voluntary disclosure of intangible value (Garcia-Meca *et al.,* 2005; Kristandl & Bontis, 2007; Singh & Kansal, 2011) may bridge information gaps, softening asymmetries, binding managerial opportunism and

easing value diffusion and sharing, with a simplifying impact even on (proper) lending contract design;

- introduction of debt covenants (Smith & Warner, 1979); for example, dividends are typically restricted in the presence of relevant intangibles (as it happens with start-ups);
- reduction of the debt's extension: operating debt, which backs intangible investments, is typically short termed, and frequent repricing, with an implicit reimbursement option for the creditor, reduces managerial discretion, easing monitoring and softening information asymmetries;
- pecking order hypothesis, where self-financing (driven by EBITDA, up to undistributed net profits) fully reflect the intangible contribution, being hierarchically preferred to (increasingly risky) debt issuance and, ultimately equity inflows;
- protection of intangibles, remembering that if intangibles can efficiently and unnoticeably be transferred by free riding managers (often with the complicity of equity-holders), then creditors may be damaged;
- proper accounting representation of the incremental impact of intangibles on the income statement, which may soften info asymmetries that traditionally concentrate on the balance sheet, where intangibles are typically under-represented.

Medtech and Biotech Companies and the Technology Transfer Cycle

Technology transfer, is the process of transferring (disseminating) technology from its place of origination. It occurs among research centres, technology parks, universities (Allen & O'Shea, 2014; De Wit-de-Vries et al., 2018), from universities to businesses, from large businesses to smaller ones, from governments to businesses, across borders, both formally and informally, and both openly and surreptitiously.

Often it occurs by concerted effort to share know-how, R&D applications (pilot projects, patents, etc.), skills, knowledge, technologies, methods of manufacturing, samples of manufacturing, among governments, universities and other institutions to ensure that scientific and technological developments are accessible to a wider range

of users who can then further develop and exploit the technology into new products, processes, applications, materials, or services.

Contractual conditions may envisage a royalty scheme, or a sale of the invention and the transfer can be eased by technological brokers. Value co-creation can be enhanced by sharing of the invention and joint development of its applications.

The technology transfer process often concerns medtech or biotech companies.

Medical technology (medtech) concerns a wide range of healthcare products and is used to treat diseases or medical conditions affecting humans. Such technologies (applications of medical science) are intended to improve the quality of healthcare delivered through earlier diagnosis, less invasive treatment options and reductions in hospital stays and rehabilitation times (Advamed, 2009). Recent advances in medical technology have also focused on cost reduction. Medical technology may broadly include medical devices, information technology, biotech, and healthcare services. Biotechnology is the use of living systems and organisms to develop or make products.

Figure 6 shows the technology transfer cycle.

The European Patent Office (EPO) has elaborated a tool called IPscore to evaluate patents, technologies and research projects.

From the EPO's last annual report (http://www.epo.org/about-us/annual-reports-statistics/annual-report/2017.html), we can draw the following trends in patenting.

Figure 6 – *Technology Transfer Cycle*

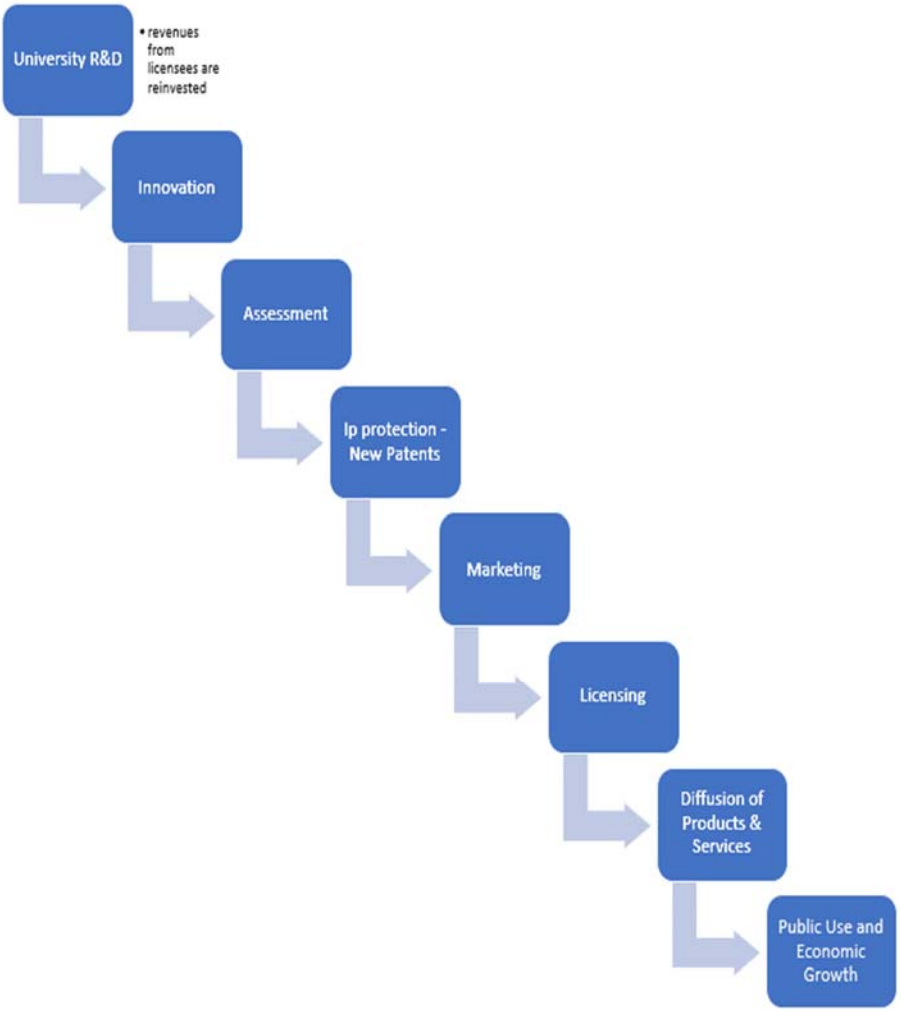
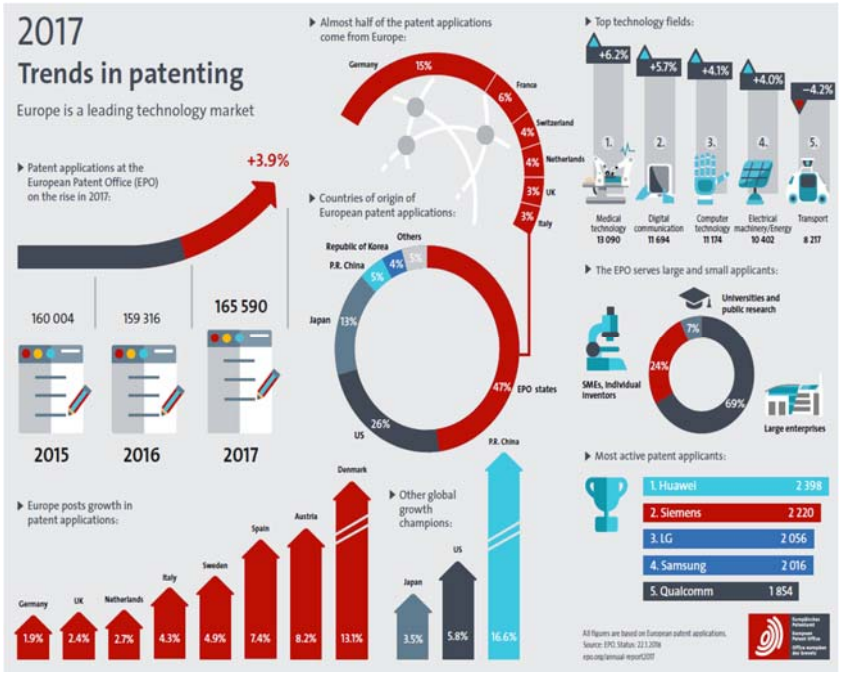


Figure 7 – *Trends in Patenting (EPO)*



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Scouting and partnership models in the early development phase

Delivering therapeutic innovation is more and more complex and challenging than ever, and how to effectively motivate and nurture innovation remains challenging for most countries and organizations. We are now live in a globalized and double-quick transforming world under the pressure of population changes, migration, internet and the social media. In the field of healthcare since priorities are continuously shifted, sustainability appears as the main issue to achieve a long term personal and population wellbeing.

Thus, a continuous effort to innovate is required. Nowadays, scientists and researchers from Academia and public institutions work together to extend the limits of knowledge. On the other front, industry needs innovation to pursuit sustainability and economic growth. To work together in an effective way, they need a convincing partnership strategy that works in areas of competitive collaboration and tremendously high innovation.

The main focus of this presentation is on early discovery and development phase of therapeutic solution. Starting from the experience in a company technology driven by small molecules original chemistry, scale up synthesis, appropriate formulation and clinical development mainly in the area of the nervous system diseases and disorders including pain.

Today, our drive in the internal research and scouting of external opportunities not only takes in consideration the innovative setting, the strong scientific rationale and the market needs, but takes into account the question: does the work we do in discovery and early development adequately reflect patient's priorities.

This is an important aspect and new and proactive players should be found to help in the task. In fact, eminent science is no more the sole

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agent in defining patients' unmet needs. And, already at the early stage in the meantime new molecular and significant achievement from the fundamental target are discussed, we need to work for meaningful, impactful and valuable treatments, thinking ahead combining good science and person priorities.

There are many and valuable definition of the innovation but to be new as single feature is not enough. Sometime finding new answers to the same question can be by itself innovative. Innovation nowadays can be obtained and sustained though collaboration. The melting pot can be an essential booster for successful innovation, but it's always matter of debate. For example: where and when the two different points of view "extend the limits of knowledge" and "pursuing the economic growth and sustainability" meet their matching counterpart? Where the two partners can meet? What is the smart occasion to create network and share elements needed to understand capabilities and to build up a free scientific exchange and a strategic partnership? How to leverage the different capabilities to pursuit a common good? How can they build and speed up an innovation process to get the success off the ground? Moreover, in which way the interaction can facilitate the introduction of societal need and allow creative solution coming from different stakeholders in an inclusive model?

Sometime in the past collaboration just meant sharing. Although, the optimization of the cost in research and development is valuable that is not enough. The most significant fuel to sustain innovation is to be successful by steps. In fact, even small innovation success is the emerged part of the iceberg where all the linked application derived elicits the long term-value. Thus, finding the right partners is essential in the early phase of therapeutic development. There are several points that are critical to create an effective partnership between academia and industrial research, firstly because the two parts are apparently committed to different missions. But the two fronts are the opposite sides of the same coin and misunderstanding the aim of the collaboration sometimes is a critical issue, if not fully clarified at the beginning. Each part should move beyond the simple exchange of "research for funding" and needs to be prepared to feel each other as a scientific, development and business partner in a fresh, dynamic and shareable innovation process, to be part of a virtuous technology transfer cycle. In the past a

successful cycle linked research economy and commercial economy. To obtain simple products or process solutions this model still is in place and works well. Thus, leveraging the capabilities from incremental technology innovation to realize new product that are able to increase sales and profits these in turn are invested in R&D resource. However, this simple model often fails to cope with the complexity of the needs and the length and the cost of the pharma product development. One of the most significant way to support the process is an open innovation model that in our experience is based on a dynamic pipeline that assesses and leverages value at any given step. The main features of the product in the development path should be innovative, feasible, reliable respectively in the discovery, early development and late development phases. In order to place patient priorities at the top of pharmaceutical development is relevant to pass from a one-size fits-all medicine towards stratified or patient individual precision medicine. This is a challenging task at early stage and in particular for a small molecules-based company. Nevertheless, it appears important to set the cultural elements in very healthcare organization that wish prioritize and support patient engagement. There are examples even for complex diseases such as Parkinson's where the today request is person-centered care beyond the patient-centered care approach. In any case the most important thing is remaining tuned on the voice of the final user of the innovation products and in the specific request and need coming from each person according to his age and conditions in a person-centered way.

An important support to companies looking toward the person needs are at the moment where the business part can find the right moment to meet governmental, academic and societal based innovators as stakeholder of the innovation process.

The Intellectual Property is the core issue of the present Technology Transfer Cycle meeting event. Confidentiality and Intellectual Property (IP) rights are the first hurdles when trying to create a partnership, in spite of the common wishes. Nowadays, these aspects are getting more challenging because of new scenarios opened to -omics, big- and crowd-data and sensitive information treatment. Entering upon a relationship requiring legal agreements that include equitable IP, developmental and commercial rights is also critical. In the recent years, concepts such as «pre-competitive», «non-competitive», «patent-free» spaces were

proposed, but they did not produce significant benefits for both parties. In an incoming era of clouded and crowd data also the IP should be efficiently non-interspersed and redistributed. We believe that establishing strategic, short and long term "integrated and win-win" partnerships is still possible. Moreover, to foster open innovation and intellectual property right at the same time is a paradox only at the first sight. In fact, a productive collaboration as well as consolidated scientific community models require a constant respect of the ownership of any single achievement, including the background know-how. One of the most common discussions comes about when patent and the timing of cooperation is a key strategic choice. The partnership or licensing can take place in one of two institutional regimes: a pre-patent period in which the scope and timing of rights is uncertain, or a post-patent period in which uncertainty about the scope of IP rights has been narrowed. The selection of the best timing together with a proper publication and diffusion strategy is important. Finding the best time allow academic and private partner to build the trust required to start and sustain a productive interaction for long term achievement.

New fields of innovation such as those based on personalized medicine, digital transformation, stem cells, genomic, microbiome offer great opportunities for public-private innovation partnerships with the goal to find and exploit new solutions.

Sabrina Moretti[7], Francesco Sacchetti[8], Giuseppina Fusco[9]

Patient engagement across companies product lifecycle development

In the recent years a cultural shift in health care and in doctor-patient relationship has begun (Sacristan 2016, Prey 2014). The enormous expansion of information technology, has urged patients to demand a more active role and participation in their own medical care, resulting in a shared decision making with their own clinician. (Sacristan 2016). While society considers now obvious the participation of patients to their own medical care, their participation to health related research still finds hurdles. Research continues to be predominantly carried out on patients which are merely seen as a source of data, and not with patients, considering their active contribution in the research process (*ivi*).

Until recently, patient engagement in biopharmaceutical and medical device development has been infrequent, episodic and restricted to the periphery, or to their direct participation to clinical trials and post-approval activities (Anand 2017). Nowadays there are specific organizations such as the *Patient-Centered Outcomes Research Institute* (PCORI), a United States-based non-profit organization, the *Agency for Healthcare Research and Quality* (AHRQ), a USA governmental Agency, and the European Medicines Agency's (EMA) *Patients' and Consumers' Working Party* (PCWP), which are actively working on designing an inclusive public health policy whose priorities will result from the dialogue of all stakeholders with the idea of a bottom up process.

There is not a distinctive definition of the concept of public engagement. Meanings attached to "public engagement" differ accordingly in different contexts and for different stakeholders. An

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analysis of existing literature, brings to a definition of patient engagement as a comprehensive process of integrated actions impacting not only those taking part to it directly, but indirect stakeholders as well, embracing a wide variety of subjects. Further, the determinants of such a process need to be appreciated in terms of the direct stakeholders rationales which are strictly dependent on to individual inter-acting interests, needs, values and objectives.

Even though there is a growing body of shared experiences of those that have performed meaningful patient engagement, there is still a lack of clear consensus on exactly how and when to optimally engage patients. This reflects the newness of this approach to research (Duffett 2017). Furthermore, there is no common agreement on what and how to measure successful outcomes of Patient Engagement (Boutin *et al*. 2017, 35).

The aim of this research project is to investigate which patient engagement activity different stakeholders apply and how Italian companies involve patients in their biotech products development process. This work is based on the literature review and on the data collected through an ongoing field research started at the end of 2017. Under a qualitative approach, our ongoing research project involve two categories of subjects: Italian R&D directors of biotech industries and representative of patient associations in Italy. We have arranged a set of in depth interviews trying to include different categories of biotech firms. We also met various categories of patients and their associations, trying to design a future comparison of the patient involvement among different research sector (e.g. diagnostics, pharmaceutics, etc.) and different illness association (e.g. cancer, epilepsy, etc).

In order to analyze the concept of patient engagement, this paper focuses on three main subjects/stakeholders interacting with each other: Patients, Regulatory Bodies, Red Biotech[10] Companies. The intent of this paper is to provide a description of the main issues regarding the actors we have identified with respect to patient engagement and begin a deconstruction of the complexity related to this concept, due to the

[10] In the medical industry it refers to Biopharmaceutical, which is defined as medical drugs that are produced by applying methods of biotechnology.

difference in various stakeholders objectives and to the relationships that exist between them in the definition of the processes of care, research and regulation.

In the following paragraphs we present the results of our analysis. We first reflect about the terminological expression "Patient Engagement", then we discuss the levels that engagement can reach, ranging from representative to advocate. We further describe the role of EMA as a regulatory agency supporting the process of inclusion of patients in the relationship with other stakeholders. Finally we present some issues about patient centricity as a companies' organizational approach, that aims to involve patients in its research and development processes and present the first results of the structured interviews we made to patient associations and biotech companies in order to understand the status of patient engagement in Italy.

1 Patients

1.1 On the terminological expression "patient engagement"

According to different authors (Boivin et al. 2014, Health Innovation Report 2014, Duffett 2017) the term "patient" means "someone (not necessarily the proper patient) who possesses experiential knowledge" The definition of patient engagement in research has varied over time and across contexts since the introduction of the term in the 1990s (Higgins 2017). Even though a consensus of what exactly constitutes a patient engagement is lacking, it is recognized that "patient engagement" encompasses a network of related concepts such as involvement, participation, activation, empowerment, adherence, compliance, health literacy, shared decision making, empathy.(Higgins 2017; Graffigna 2017; Duffett 2017). The complexity of the definition for "patient engagement" and the broad range of levels of engagement has led to a variety of terms used to identify any person or group of persons having a "stake" in the outcomes of the research. Some research groups use the term "patients", while others use terms such as citizen, public, end users, or stakeholder (including patients, clinicians, policy makers, payers, etc.). EMA for example defines a «patient (or patient representative)" involved in the benefit-risk evaluation process as "an

individual, patient, carer or parent representing patients, not an individual representing a specific organization» (EMA 2014, 2). While the term "patients" in McGinnis *et al.* 2013 always refers to patients, family and other caregivers, consumers and the public In the same way Carman and Workman (2013), define patient and family engagement as patients, families, patients organizations, and health professionals working in active partnership at various levels across the health care system – direct care, organizational design and governance, and policy making – to improve health and health care. In addition, each individual research context requires a precise group of patients to engage (individual experience patients, members of the general public or patient organizations). (Duffett 2017).

1.2 On Engagement/Involvement

The two terms imply a different perspective and idea about the role of the patient in (research?). As noted by Hoos and colleagues: the «selection of the term patient involvement rather than patient empowerment or patient engagement is deliberate and intentionally captures the central role that patients should play in medicines development and lifecycle management. Involvement reflects the need for patients to be active participants – valued and valuable partners – whose input, advice, and guidance is sought and implemented throughout the process. Today, a lot of different terms are used, and often the same terms are used while being differently defined or intended. This adds to and maintains the confusion» (Hoos *et al.* 2015, 2). According to Kearney and colleagues (2017) 'engagement' has a more passive connotation than 'involvement', the former being a model in which patients or the public are receivers of information or education rather than being active contributors.

Some authors state that the term "engagement" implies patients participation during the research process: «the term "engagement" means when patients co-build research programs through meaningful and equal partnerships with clinicians, scientists and other research team members. This type of patient engagement should occur throughout the entire lifecycle of research» (Duffett 2017 114).

There is anyway general agreement in literature that patient engagement is an essential aspect in the research and development of biopharmaceutical products and in the management of a disease. The improvement of the lives of patients requires a deep understanding of their medical conditions, experiences, needs and priorities, and of their relationships with the family and their caregivers. However, there is no agreement on the semantic aspect of the expression "patient engagement". This semantic dispersion is an indicator of the fact that there is not yet shared practices among the various stakeholders that still recognize the patient engagement as a fundamental element in the health landscape of the contemporary world.

1.3 On the levels of patient expertise for engagement

Whereas clinicians, scientists, and healthcare professionals have disease specific expertise, patients have experience based expertise (Boivin *et al.* 2014; Health Innovation Report 2014; Duffett 2017). «Experience based expertise is the skills and knowledge that is derived from personal experiences, such as living with a chronic illness and coping with the daily management required, and its impact on one's life» (Duffett 2017, 114).

In order to evaluate patients experience based knowledge, literature evidence strongly suggests the importance of the creation of spaces and practices for patient inside the scientific research institutions, that allow them to be actively involved and to contribute in different phases of a medical product lifecycle development (drugs, protocols, medical devices, etc.). The level of engagement is of great importance and it could vary from a mere presence of the patient as representative without an active role (without equal authority as others subjects), to taking actively part in controlling, directing, and managing the research (table 1). The levels of patient engagement in the research process are strictly dependent on individual desires and capabilities, partnering competences with providers and institutions and the social, economical and political organization of the patient living environment (Higgins 2017; Graffigna 2017).

Table 1

Levels of engagement in research	Description	Example
Representative	Present but not an active participant	A patient or patient group that is invited to be present at a meeting but primarily as a passive role and without equal authority as others present.
Consultant	Providing input and views on a select aspect of research but still external to the research team	A patient participates in a focus group or completes a survey about an aspect of the research, but no other involvement with research team or decisions made.
Partnership	Equal partnership with research team, given opportunity to provide meaningful contributions and co-building of research	A patient is fully incorporated into the research team and contributes to the development of the research questions, clinical trial design, trial execution, and dissemination of results. The patient is acknowledged for contributions as a co-investigator.
Leadership	Actively controlling, directing, and managing the research	A patient is the lead investigator, responsible for developing the research either solely or as co-principle investigator with traditional researchers.
Advocate	Focus on patients' rights, lobbying for changes, often with a specific agenda	A patient or patient organization that lobbies the government for increased funding for research.

(In Duffett 2017, 115)

1.4 In our ongoing research with patient organizations

In our ongoing research with patient organizations we found that in Italy patient engagement is on its early stage, fragmented in a multitude of local small activities and projects. From our interviews in the field of chronic diseases, the use of healthcare professionals as proxy is seen as a more appropriate solution rather than the engagement of patients. We register some initiatives of patient engagement as representatives or consultants in meetings without an active role. In some occasions patients were asked to respond to questionnaires about their illness experience. Few projects about outcomes evaluation are present, but only on approved drugs,without considering early stage research and development of the product. But we are still continuing to monitor experiences and perspectives of associations to enlarge our sample.

In our research we also met the European Patients' Academy (EUPATI) Italian Group which is focused on the education of Italian

patients and encourage their involvement in the process of new medicines development, promoting informed lifestyle choices, risk-factor modification and active patient self-management. EUPATI is a 5-year public/private partnership funded by the Innovative Medicines Initiative (IMI) in February 2012. It is patient-led, coordinated by the European Patients' Forum (EPF), with other public bodies (European AIDS Treatment Group EATG, Patients Network for Medical Research and Health EGAN and EURORDIS-Rare Diseases Europe) in key roles. The Italian group underlines that we are at the beginning of patient engagement in our country, but they have a strong motivation to educate and inform patients because they strongly believe that active participation is achieved solely by well-trained-infrormed patients, aware of the whole research process from its beginnings. The main goal is to provide scientifically reliable, objective, comprehensive information to patients on pharmaceutical R&D. This will increase the capacity of well-informed patients to be effective advocates and advisors in pharmaceutical development with regulatory authorities, companies and other stakeholders.

2 Regulatory Bodies

National health services consider nowadays of increasingly importance to actively involve patients in the identification of health priorities following the assumption "nothing about patients, without patients" » (Pushparajah, 2017, p. 7).

In 2006 the European Medicines Agency (EMA) constituted the Patients' and Consumers' Working Party (PCWP) which recently confirmed the commitment at improving patient engagement to ensure that patient «views and needs are taken into account at every step» of medicines lifecycle development (EMA 2015,). The EMA and the Heads of Medicines Agencies (HMA) strategies for the period up to 2020 underline the need for a patient focused innovation in which they declare that «in order to stimulate development, there is a need to facilitate the translation of scientific advance into innovative medicinal products that meet regulatory standards, accelerate patients' access to innovative therapies with added valued for patients and are affordable to the EU Member States' health systems» (EMA and HMA 2015, 10). One of the three focus areas of the EMA's Committee for Medicinal Products for Human Use (CHMP) is the «involvement of patients in the assessment of the benefits and risks of medicines», and it also provide guidance for

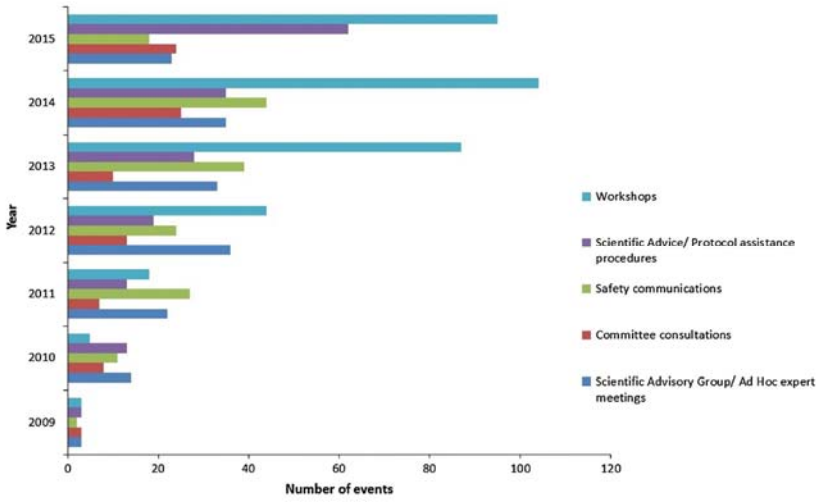
EMA Scientific Committees on incorporating patients' views during these assessments (EMA 2016).

Current patient involvement at EMA consists of the participation of patients/consumers as members, alternates or observers in activities involving individual patient/consumer experts or activities requiring organization representatives. Figure 1 shows that the number of EMA events participated by patients or patient organizations have increased over the years. This demonstrates the interest of EMA in strengthing a closer collaboration with patients (Pushparajah 2018). In addition, real-life experiences of patients is being increasingly embedded in the regulatory output produced by the European Medicines Agency.

There is a growing number of initiatives to form and train patient advocates in order to become valuable partners of health stakeholders and provide useful information that can help shaping the medicine lifecycle development from early research to commercial activities after marketing authorization (Pushparajah 2018).

Figure 1. shows the increasing number of patient involvement in EMA events as and their participation expansion in training activities.

Figure 1. EMA increasing events and boards in which patient is required to participate



(In Pushparajah 2018 - Moulon, I. 23 June 2014, Cooperation between EMA and patients' and healthcare professionals' organisations).

3 Red Biotech Companies

The development of a pharmaceutical product is a multistage process which includes the identification of a research question, the application for fundings and ethical approval, an advisory board engagement, the realization of the research, the dissemination of the research findings (Hayes et al. 2012).

Red Biotech companies are recently trying to develop a new organizational and business perspective based on patient centricity rather than a disease centered approach in the whole process of a pharmaceutical product development (Higging 2017). From this perspective, the development of new drugs using a patient-centric approach can provide an opportunity to more closely meet patient needs and improve their lives in an added meaningful perspective for them and their families (Yeoman et al. 2017).

As Yeoman et al. 2017, 2.explain in their paper the advantages of a patient centered approach for companies are numerous «Working with patients fosters innovation and it will ensure that the objectives of patients are met early on in the biopharmaceutical development process by incorporating their views and needs, leading to more impactful patient outcomes. Patients are the ultimate end users of medicines and it is they and their carers that should prioritize their needs and identify the outcomes that they desire. In this respect, patients should be given the opportunity to define their needs, including the value of interventions, the benefit and risk trade-offs based on their values, their desired clinical outcomes, preferences and experiences» In this process policy makers and payers seek to control costs by requiring evidence of value and comparative effectiveness, compelling healthcare providers to focus on patient impact. So patient centricity is also an issue of sustainability of the product lifecycle.

Many authors report positive impacts of patient engagement in research under the organizational form of patient centricity: improved relevance of research to patient priorities, significant contributions to trial design (deciding on comparators, outcomes, protocols), improved patient information material and/or informed consent documents, improved clinical trial enrollment and decreased attrition, improved dissemination and/or implementation of research findings, and

increased public trust in research (Duffett, 2017; Caron-Flinterman 2005). Lastly ethical arguments consider health research a democratic political process, favoring the participation of patients in the research process by virtue of a moral (Serrano-Aguilar et al. 2009).

Nonetheless many factors contribute to the skepticism/doubts towards patient engagement in many pharmaceutical industries: uncertainty about patients' ability to contribute in research, additional costs, slowing down and interfering with the research process, uncertainty on how to resolve conflicts, confusion around how to operazionalize a patient-centric approach, uncertainty around the financial value that patient-centricity provides (Levitan et al. 2017; Duffett 2017). One of the biggest obstacles to sponsor engagement with patient groups is a lack of well-defined best practices and guidelines. Often there are no guidelines at all for engagement activities within a particular company, and tracing new routes can take a long time and compete with other research/business priorities. On the other hand many patients think that their role in research is merely symbolic, often referred to as "tokenism", or to provide a false appearance of inclusiveness (Duffett 2017).Thus patient engagement is often limited to clinical trial participation or education about a new drug with healthcare professionals used as proxy (Yeoman 2017).

3.1 In our ongoing research on Italian Red Biotech companies

In our ongoing research on Italian Red Biotech companies the respondents to our interviews recognize the strategic role of patient knowledge share to reach better outcome, but they also emphasize some burocratic negative elements in the full accomplishment of this new patient centered organization. They advocate the importance of a cultural change inside organizations and companies to hold the line with regulatory new requirements on patients engagement and to ensure that the developed pharmaceutical products meet the exact needs of their target patients.

One of the main aspects regarding the interest of Italian companies for patient centricity approaches is the sustainability of the research and of the development process. In an extremely competitive environment and with the advances in medical knowledge, a "One Drug Fits For All" development, which worked decades ago, is no longer sustainable. A

drug nowadays is 10 times more active than it was 20 years ago and it has become more difficult to identify a new one with a significative active difference. Companies, especially small-medium ones are therefore moving their business to personalized medicine and rare genetic disorder drugs development which involve smaller groups of patients with specific characteristics and unmet needs. This inevitably highlights advantages for companies in patient engagement for medicine lifecycle development.

Conclusions

The concept of patient engagement underlines the need for integration between a disease scientific expertise and an experience based expertise. In this sense patients should be involved in the identification of health priorities and outcomes. However the level of patient engagement could vary significantly due to personal and external factor, such as the ability of other stakeholders to involve them in research and development processes.

EMA has constantly increased the concrete participation of patients within it, with peer authority in the discussion tables with other stakeholders. This has allowed EMA to gather the knowledge and preferences of patients at every stage of the process, embedding real-life experiences of patients in regulatory outputs.

Companies interpret patient engagement as patient centricity, a new organizational model which includes patient experiential knowledge in research and development processes. This means to shift from a disease-centered to a patient centered model and as a consequence to constantly interact with regulatory agencies and their request for a patient centered outcome.

Interrelationship between this three stakeholders is shaping the landscape of contemporary healthcare research and development. Each of them in various forms is involved in a process of organization and perspective change. Furthermore this process could be seen as a cultural change because of its ties on identity, practices and goals of each actors/organizations. Although culture and process change cannot happen in a short period of time, the demand for patient-relevant/patient-centered outcomes by regulatory bodies could be seen as a rule governed moves toward patient engagement. Despite this, there

are no common or shared best practices and protocols, and companies and patient organizations initiatives are generally sporadic and inconsistent, which impede their effectiveness. In the Italian context, as well in all western countries, Patient engagement is seen as a fundamental process, but its implementation is still a learning by doing performance.

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