PROTEIN STABILISERS: NEW OPPORTUNITIES FROM PATENT EXPIRY

MIBio 2012, Cambridge

Arthur Lallement & the CambridgeIP team

CAMBRIDGE IP
TECHNOLOGY INTELLIGENCE. OPEN INNOVATION. IP STRATEGY
WWW.CAMBRIDGEIP.COM | WWW.BOLIVEN.COM

Introduction

- Patenting trends in the Biopharmaceuticals stabilisers space
- Completing our research presented at the 2011 Biosimilar symposium at Bloomberg, London.
- **Motivation:** The first patents protecting biopharmaceutical formulation stabilisers have already expired, potentially opening new opportunities.
- **Method:** CambridgeIP built a comprehensive dataset including **751 US and European granted patents published before 1995**. In addition, we analysed an antibody subset of 100 patents.
- **Research boundary:** Most of the analysed patents describe formulations, fewer patents describe methods. Patents referring to manufacturing processes, hybridization, detections and assays have been excluded from this search.
- **Our definition of biologic drugs** is based on scientific assumptions rather than legal statements.

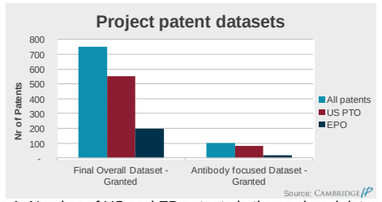

Figure 1: Number of US and EP patents in the analysed dataset

Figure 2: APIs included in the search string

- The biopharmaceutical space experienced exponential growth in the 1980's.
- To address the stability of biopharmaceuticals, formulation patents claiming the use of molecules stabilising the therapeutic agents were filled very early.

Stabilisers patenting study

Our study identifies key Corporations, Research Institutes and Individual researchers, together with their R&D collaborations. Our study additionally provides insights into industry wide trends and specific corporate IP strategies.

- Stabilising effects have been patented as early as 1930's with hormone formulations.
- In the 1940's the interest switched to cholinesterase with patents filed by Sterling Drug Inc.

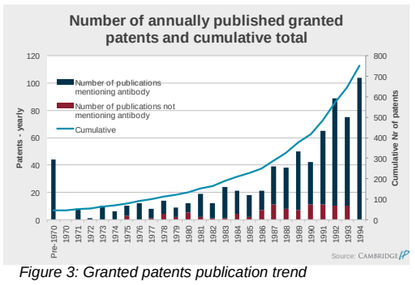

Figure 3: Granted patents publication trend

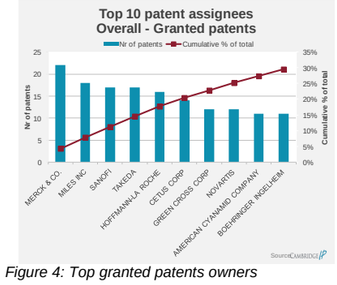

Figure 4: Top granted patents owners

1. **Merck & Co.** first granted patent was published in 1963 (polio virus) and the other patents protect stabilised formulations on vaccines, spacers, dipeptide moiety, plasminogen and Fibroblast Growth Factor.
2. **Miles Inc.** first granted patent published in 1971 (Stabilized aluminium hydroxide suspensions) and the other patents protect stabilised formulations on Alpha -1-proteinase, immune globin, pasteurized protein compositions and blood factor.
3. **Sanofi** first granted patent published in 1984 (Somatocrinin) and the other patents protect stabilised formulations on somatocrinin and glycoproteins.

		Selected stabilisers					
	Total	Glucan sulfate	Albumin	Polyethylene glycol	Polyvinylpyrrolidone	Encapsulation/ microsphere	Conjugation
Total	751	4	108	55	13	16	49
APIs Enzymes	165	0	13	7	1	5	15
Cytokines	89	0	27	10	2	1	1
Peptidic Hormones	92	0	14	12	2	7	1
Growth factors	54	4	8	3	1	4	0
Antibodies/Ig	154	0	26	16	1	1	24
Epitopes	2	0	0	1	0	0	1
Nucleotides	50	0	4	3	0	1	4
Nucleic acids	42	0	3	2	0	3	2
Vaccines	54	0	11	2	0	0	7

Table 1: Technology matrix highlighting blank and congested spaces

- Of the stabilising technologies that have been selected above, albumin is the most often claimed.
- Another stabilising technology often claimed prior to 1995 is conjugation.
- Antibodies and cytokines have been patented a lot with albumin and polyethylene glycol (PEG) stabilisers.
- Polyvinylpyrolidone has not been as patented as PEG.

Index	Name	Nr of patents	Organisational affiliation
1	FERNANDES PETER M	7	CETUS CORP, CUTTER LABORATORIES, MILES INC
2	KOTITSCHKE RONALD	6	BIOTEST PHARMA, BIOTEST-SERUM-INSTITUT GMBH
3	LUNDBLAD JOHN L	5	CUTTER LABORATORIES, MILES INC
4	MITRA GAUTAM	5	MILES INC, CUTTER LABORATORIES
5	STEPHAN WOLFGANG	5	BIOTEST-SERUM-INSTITUT GMBH, BIOTEST PHARMA
6	UEMURA YAHIRO	4	GREEN CROSS CORP
7	BOTT RICHARD RAY	3	HOFFMANN-LA ROCHE, GENENCOR INTERNATIONAL INC
8	COUSENS LAWRENCE S	3	NOVARTIS
9	DEMARNE HENRI	3	SANOFI
10	EIBL JOHANN DR	3	IMMUNO AG

Table 2: Top Inventors in the stabilisers biopharmaceutical space according to the US and EP granted patents

Several of the top inventors are affiliated with Miles Inc (renamed under the North American division of Bayer AG, 1995) as shown above. All these inventors are also affiliated to Cutter Laboratories, as Miles also owned Cutter Biologicals, a manufacturer of diverse products such as insect repellent and synthetic human Factor VIII clotting factor for haemophiliacs.

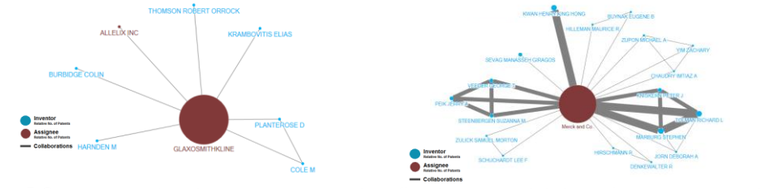

Figure 5: 2 assignee-inventor network analyses showing two different development strategies: In-house development for Merck & Co and collaborative developments for Glaxosmithkline

# forward ref.	Publication number	Patent assignee	Legal Status	Title	Abstract	Application date	API	Selected claims on the stabilising effect
294	US4925673A	CLINICAL TECHNOLOGIES ASSOCIATES INC	Reassigned to EMISPHERE TECHNOLOGIES, INC. in 1992. The patent expired in 2002 due to the non payment of fees. Although, in 2005 it was reassigned to MHR INSTITUTIONAL PARTNERS LP, NEW YORK	Delivery systems for pharmacological agents encapsulated with proteinoids	Methods are described for targeting the release of an active pharmacological agent in an animal by administering that agent encapsulated in proteinoid microspheres which are stable to the environment encountered from the point of introduction until they migrate to the targeted body organs, fluids or cells and are there unstable. Orally administered delivery systems for insulin, heparin and physostigmine which encapsulating microspheres which are predominantly of less than about 10 microns in diameter and pass readily through the gastrointestinal mucosa and which are made of an acidic proteinoid that is stable and unaffected by stomach enzymes and acid, but which releases the microencapsulated agent in pharmacologically active form in the near neutral blood stream. Basic proteinoid microspheres encapsulating a dopamine redox carrier system are administered in the weakly basic, where they are stable, and then enter the blood stream, where the encapsulated agent is similarly released.	1987-08-08	Insulin, heparin, physostigmine	2. Composition of claim 1 wherein said microspheres are stable in at least a segment of the gastrointestinal tract, are unstable in the blood stream and are predominantly less than about 10 microns in diameter so as to readily penetrate the gastrointestinal mucosa and release said active agent in the blood stream in physiologically active form. 15. Method for producing an orally administerable composition for delivering insulin to the blood stream in physiologically active form comprising mixing insulin with water and contacting said mixture with a thermal condensation polymer derived from about two parts glutamic acid, about two parts aspartic acid and about one part of neutral or basic alpha-aminoacid.
132	US5359030A	PROTEIN DELIVERY INC	Reassigned to LAI VENTURES, INC., MINNESOTA in 1996 then NOBEX CORPORATION, NORTH CAROLINA in 2000, then BIOCON LIMITED, INDIA in 2005. Fees have been paid until expiry.	Conjugation-stabilized polypeptide compositions, therapeutic delivery and diagnostic formulations comprising same, and method of making and using the same	A stabilized conjugated peptide complex comprising a peptide conjugatively coupled to a polymer including lipophilic and hydrophilic moieties, wherein the peptide may for example be selected from the group consisting of [see API column]. In a particular aspect, the invention comprises an insulin composition suitable for parenteral as well as non-parenteral administration, preferably oral or parenteral-administration, comprising insulin covalently coupled with a polymer including (i) a linear polyalkylene glycol moiety and (ii) a lipophilic moiety, wherein the insulin, the linear polyalkylene glycol moiety and the lipophilic moiety are conformationally arranged in relation to one another such that the insulin in the composition has an enhanced in vivo resistance to enzymatic degradation, relative to insulin alone. One, two, or three polymer constituents may be covalently attached to the insulin molecule, with one polymer constituent being preferred. [...]	1993-05-10	selected from the group consisting of insulin, calcitonin, ACTH, glucagon, somatostatin, somatotropin, somatomedin, parathyroid hormone, erythropoietin, [...]	15. A stable, aqueously soluble, conjugated peptide complex comprising a peptide stabilizingly and conjugatively coupled to a polyethylene glycol modified glycolipid moiety.
28	US5208041A	ALLELIX BIOPHARMACEUTICALS INC; GLAXO CANADA	Co assignement, fees paid	Essentially pure human parathyroid hormone	human parathyroid hormone is provided in an ultrapure form characterized by the absence of protein contaminants detectable by capillary electrophoresis analysis. A method for obtaining such ultrapure human parathyroid hormone is also described.	1991-05-23	human parathyroid hormone	8. A pharmaceutical composition according to claim 5, further comprising a stability-enhancing amount of a reducing agent.

Table 3: Selected top cited patents,relevant claims, and legal statuses

Methodology

- Literature review of Biopharmaceutical formulation patent literature published before 1995
- Interview of biopharmaceutical and industry experts
- Development of technology matrices informing semi-automated and expert-validated analysis of the patent space on Boliven® systems, generation of trend information and identification of examples
  - ✓ Report samples are available on Boliven.com (free registration for access): www.boliven.com/landscapes
  - ✓ Further research data and analysis is available on request

KEY FINDINGS

- A vast library of prior art exists on biopharmaceutical stabilisers, which can be integrated into innovative technologies
- Inventors in this space tend to patent with a single company.
- Collaborations which emerge from the assignee-inventor network diagram are centred around Japan and Boston – areas which are pioneers in the development of technology clusters

Focus 1 - Antibodies subspace

Antibody formulations stabilisation stated to be patented in the 1970's.

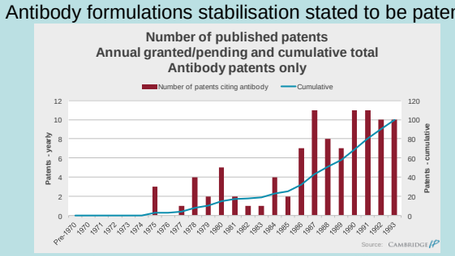

Figure 5: US and EP granted antibody patents filling trend

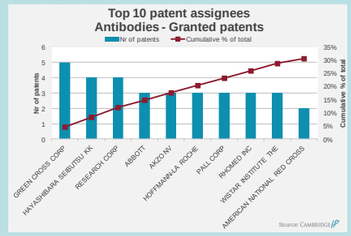

Figure 6: Top patent owners in the antibody stabilisers subspace

In 1995, the top player in this space was green cross with patents granted in the fields of *pseudomonas aeruginosa* treatments, gama globulin preparations and immunoiglobin injections.

# Forward references	Publication number	Patent assignee	Legal Status	Title	Abstract	Application date	API	Selected claims on the stabilising effect
159	US4741900A	CYTOGEN CORP	Fees paid	Antibody-metal ion complexes	This invention relates to antibody-metal ion complexes having a metal ion coordinately bound to a compatible chelator covalently bound to an antibody or antibody fragment. Also described are methods for intermediates in the preparation of antibody-metal ion complexes. Therapeutic and in vitro and in vivo diagnostic methods utilizing such antibody-metal ion complexes are described.	1984-08-31	monoclonal antibody or monoclonal antibody fragment	10. The method according to claim 1, wherein the antibody-chelator conjugate is stabilized by exposure to an effective amount of a reducing agent.

Table 4: Third top cited patents in the antibody subspace.

A shown above, one of the top cited patents that has been maintained until its expiration claimed an antibody chelator conjugate to stabilize an antibody-metal ion complex. This patent has been cited by 159 later patents.

Focus 2 - Takeda

Takeda API formulations mentioning some stabilising properties published before 1995 focus on:

- Fibroblast growth factor (FGF)
- mAb
- Interleukin
- Superoxide dismutase (SOD)
- Gamma-interferon
- Thyrotropin releasing hormone
- Attenuation of mumps virus

# Forward references	Publication number	Patent assignee	Legal Status	Title	Abstract	Application date	API	Selected claims on the stabilising effect
14	US5314872A	TAKEDA CHEMICAL INDUSTRIES LTD	Fees paid until 2002, then lapsed due to non payment of fees	Glucan sulfate stabilized fibroblast growth factor composition	Fibroblast growth factor (FGF) or a mutein of FGF is stabilized by bringing FGF or a mutein of FGF into contact with a glucan sulfate in an aqueous medium.Thus obtained composition comprising (a) FGF or a mutein of FGF and (b) a glucan sulfate is stabilized, so that it can be advantageously administered to warm-blooded animals.	1989-06-02	fibroblast growth factor (FGF) or a mutein	1. A stabilized composition which comprises fibroblast growth factor (FGF) or a mutein consisting of a deletion mutein of FGF and a substitution mutein of FGF which exhibits pharmacological or physiological activities similar to those of FGF and a stabilizing amount of a glucan sulfate. PO,36

Table 5: Takeda selected patent: Fibroblast Growth Factor stabilised formulation

Takeda successfully protected many stabilized biopharmaceutical formulations prior to 1995, one of the biggest family from which the patent above has been selected is protecting an FGF formulation. Although, the patent from this family have been abandoned before the expiration date in the early 2000's.

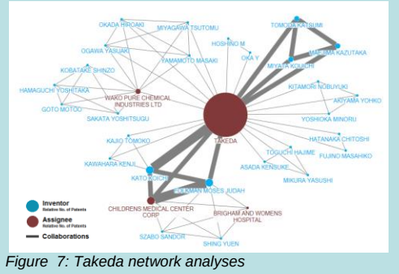

Figure 7: Takeda network analyses

The network analysis on the left shows the highly collaborative strategy of Takeda with other Japanese companies (Wako Pure Chemical Industries) and also with American organisations (Childrens Medical Center Corp).

The high level of collaborations on Takeda's IP is due to its strategic aims to produce products on behalf of partners in addition to their proprietary developments.

Contact us for more detail on our study findings: Arthur.lallement@cambridgeip.com

References

Tannock et al, (2011), *The emerging biosimilars industry: a patent perspective*
Boliven.com (2011), *Recent trends in Biopharmaceuticals patenting January 2005 to May 2011.* Iliev, Tannock
Lallement, Iliev, (2009) *The HFA pMDI Patent Landscape: Minefield or Goldmine*