Outlook of Protein Formulation Technologies

Opportunities for IV to SubQ Conversion

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Advisors

MEHTA PARTNERS

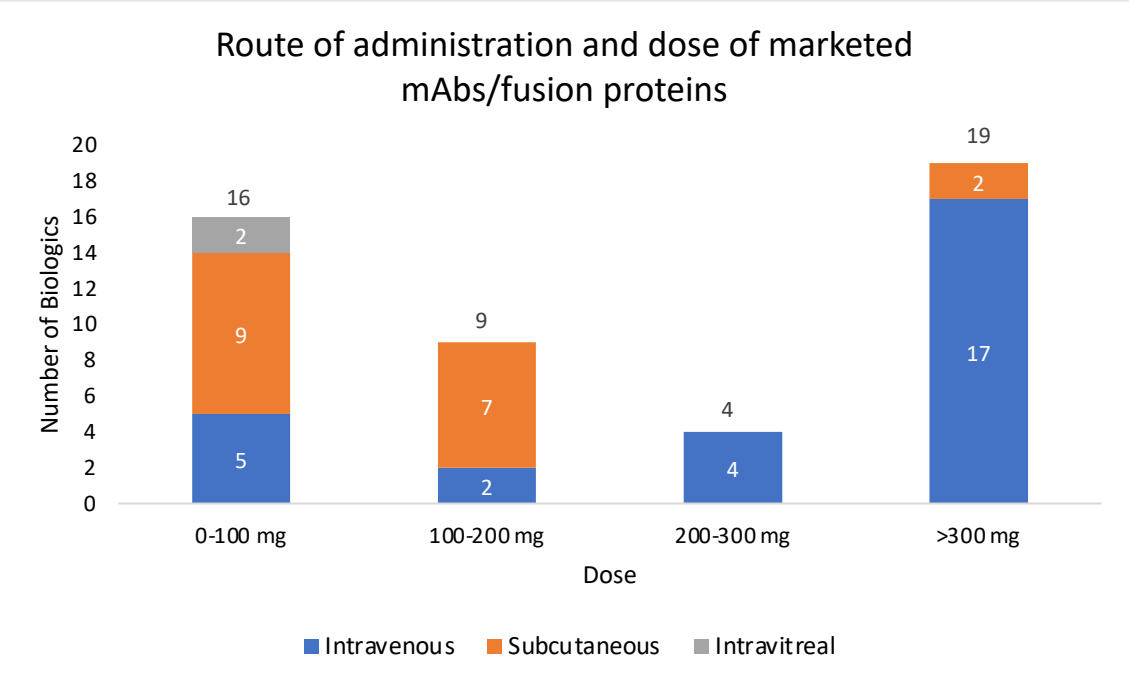
Table Of Contents

Executive Summary

- Today, ~80% of biologics are administered intravenously (IV) due to high doses and formulation development challenges
    - As a result, patients are tethered to infusion set up for hours, few times a month, often in a clinic or hospital adding significant cost
- Majority of biotechs are facing challenges in formulating high concentration proteins for subcutaneous (SC) delivery due to dearth of available technologies
- However, in the recent times, a few technologies have emerged that attempt to address the biologics formulation challenges, facilitating conversion of IV to SC delivery; they work on 2 key principles as discussed below
- **Enzyme Based Technology –** Temporarily clears the space under skin to enable administration of higher volumes subcutaneously, for e.g. Halozyme, Inc. and Alteogen, Inc.
    - The key disadvantages are inherent toxicity associated with the enzyme, prevention of patient self-administration and high cost burden
- **Viscosity Reducing Technology –** Enables high concentration by reducing viscosity, for e.g. Bhami Research Lab (BRL), Reform Bio, Excelse Bio, Arsia Therapeutics and Arecor
- Additionally, these technologies offer the added advantages like competitive differentiation and new IP for potential lifecycle management
- While most of these technologies have several disadvantages such as limited applicability across the range of biologics, non-standard formulation development process, toxicity concerns, etc. BRL offers the most promising solution amongst all
- BRL's technology comprises of two GRAS (Generally recognized as safe) category excipients – Nicotinic acid and Tryptophan
- The key features are – Concentration in excess of 250 mg/mL, viscosity in the ranges of 20-25 cP, applicable across wide range of biologics, high stability, no safety concerns and potential ophthalmic application and a global IP

Overview Of Biologics Administration

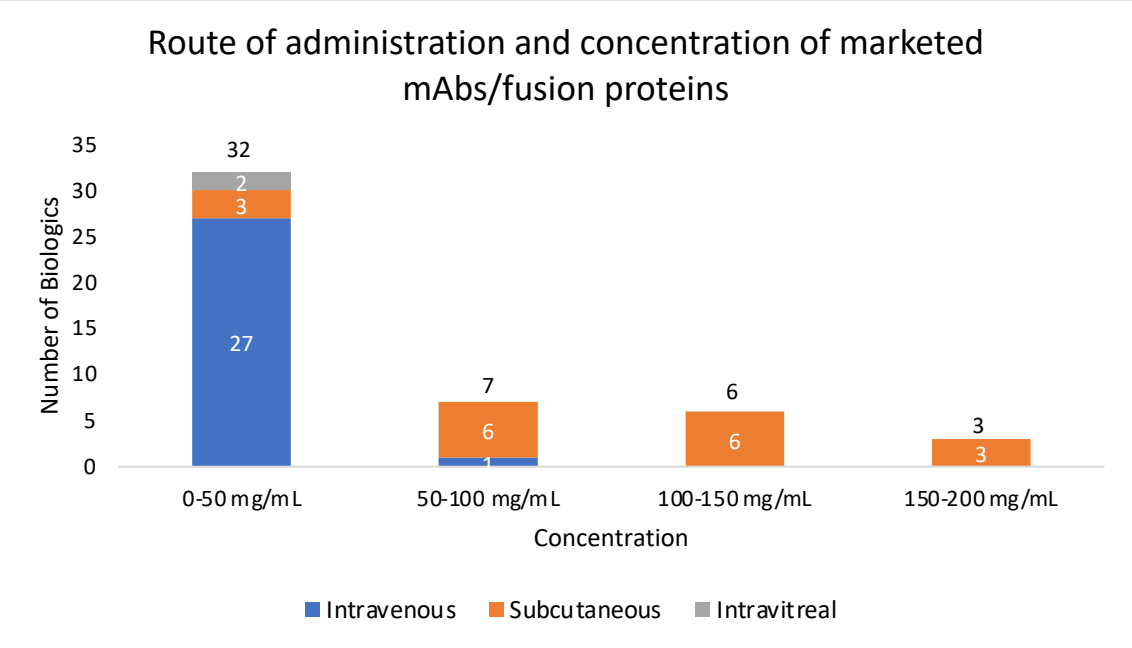
- Currently 104 of the ~130 commercially available biologics (mAbs and fusion proteins) are administered intravenously
- ~50% therapeutic protein consists of high doses (>200 mg), and thus needs high volume of 5 to 100 ml administered intravenously
- Such IV infusion can take a long time to infuse (30 min-6 hours), often in a hospital or a clinic, and several times a week leading to patient inconvenience and high cost of administration ($750-2700/cycle in the US)
- However, subcutaneous (SC) administration will be able to address most challenges associated with IV



Source: Secondary Research, MP Analysis

Challenges With Developing Subcutaneous Formulations

- Subcutaneous injection volumes have typically been limited to <2 mL of solution due to the restrictions of the extracellular matrix in the SC space
- Greater volumes can cause discomfort, an increased possibility of injection site leakage following needle retractions, swelling and injection site hardness
- The industry is facing challenges in bringing down the volumes of the formulation; high concentration formulations cause:
    - Aggregation, sub-visible and visible particle formation leading to product instability and increased risk of embolism
    - High viscosity impacting syringe ability, injection time, functionality of devices, etc. and leads to increased tissue back-pressure and injection pain.
    - Manufacturing challenges such as high shear stress during pumping, high back-pressure and clogging of membranes



Only a few companies have started achieving concentrations > 150 mg/mL like Actemra (Tocilizumab, Genentech) -180 mg/mL, Benlysta (Belimumab, GSK)-200 mg/mL, and Cimzia (Certolizumab Pegol, UCB)-200 mg/mL, that too for a handful of molecules. However, majority of biotechs still lack the technical know-how.

Source: Secondary Research, MP Analysis

Desired Properties Of The Ideal Protein Formulation

The ideal protein formulation would be a high concentration low viscosity aqueous formulation that enables subcutaneous injection.

Stability

- Stable, without aggregation, sub-visible and visible particle formation
- Buffered with pH between 6-7.5

Administration

- SC injection with 27-31G needle
- Preferred volume - 1-2 ml
- Viscosity below 50cP, preferred between 20-25cP

Formulation Technology

- A technology enabling IV to SC conversion for most proteins using the same excipients
  - Depending on the dose, the ideal concentration may range from 200-250 mg/mL
- Pharmaceutically accepted and non-toxic excipients

Industry Wide Effort To Formulate High Concentration Biologics

The biopharma industry has tried the following processes for SC administration with limited success to-date:

- **Enzyme based technology:** Temporarily clears space under the skin to enable high volume injections and spreading of injected drugs
- **Viscosity reducing technology**: Enables high concentration by reducing viscosity with excipients like
  - Surfactants (e.g., polysorbate 20 and 80), carbohydrates (e.g., cyclodextrin derivatives) and amino acids (e.g., arginine and histidine)
  - Stabilizers - acetate and succinate, carbonate, citrate, histidine, or phosphate buffers
  - Sugar or salt solutions such as NaCl
- **Suspension technology:** Utilization of particle/microparticulate suspensions to produce concentrated, low viscosity formulations. Suspensions have high risk of immunogenicity and isn't the preferred method of increasing concentration

However, a few technologies have emerged in the recent years addressing the unmet need for improved biologic formulations as discussed in the next slide.

Key Technologies Trying To Address Protein Formulation Challenges

Parameters	Halozyme	Alteogen	Bhami Research Lab	Reform Biologics	Excelse Bio	Arecor	Arsia Therapeutics
Technology Principle	**Enzyme based technology to temporarily clear space under the skin and increase absorption of injected drugs**		**Viscosity Reducing excipients to formulate high concentration biologics**				
Lead Compound	Hyaluronidase (Approved drug)	Hyaluronidase	Nicotinic Acid + Tryptophan – GRAS ingredient	Caffeine	Amino Acids	Oligomers of ethyleneimine	Camphorsulfonic acid derivatives
Amount Of Excipient Needed	75 to 150 USP units	N/A	16 mg (HGG Conc. 270 mg) – 75% Reduction in Viscosity	22 mg (BGG Conc. 280 mg/mL) – 37% Reduction in Viscosity	No standardized protocol established yet	0.2 mg/mL to about 5 mg/mL	93 mg (BGG Conc. 260 mg) – 44% Reduction in Viscosity
Viscosity Reduction	Viscosity is not an issue since large volume can be injected	Viscosity is not an issue since large volume can be injected	Works on all the tested proteins	Works on a limited number of tested proteins	Works on a limited number of tested proteins	N/A	Works on a limited number of tested proteins
Stability	Stable for 2 years at 4°C	Higher thermal stability as compared to wild type human hyaluronidase	6 months at 4 and 25°C. Further studies on-going	No stability data available	No long term stability data available	6 months at 40°C	100 days at 4°C and 7 days at RT.
Toxicity	Thrombosis or hypersensitivity reaction during injection	Lower risk of toxicity shown as compared to wild type human hyaluronidase	No toxicity. These excipients are extensively used in parenteral formulation	Serious toxicity was seen blood concentration of $\geq$ 50 mg/L	No toxicological data available	Higher the size of oligomer, higher the cytotoxic effect	Toxicology data available with limited CSA derivates
Available For Partnership	Yes	Yes	Yes	Yes	Yes	Yes	No
Ophthalmic Use	No	No	Yes	No	No	No	No

Source: Company reports, Secondary Research, MP Analysis

Enzyme Based Technologies

Halozyme

NASDAQ: HALO
Market Cap: $3.79 B

Halozyme, based out of San Diego, California, was founded in 1998 and went public in 2004.

Technology:

Halozyme has an enzyme based ENHANZE drug delivery technology that uses patented recombinant human hyaluronidase PH20 enzyme to degrade hyaluronan in the subcutaneous space. Hyaluronan is a glycosaminoglycan, a chain of natural sugars that is a component of normal tissue, such as skin and cartilage.

The effects of rHuPH20 are local and transient. By degrading HA, rHuPH20 facilitates the dispersion and absorption of other drugs and fluids that are injected under the skin allowing large volumes to be delivered in a single injection.

Key advantages of the technology:

- Lifecycle extension for originators, Potential evasion of litigation for biosimilar companies
- Successful partnership history, 5 approved products in partnership with leading pharmaceutical companies

Challenges:

- Not effective in increasing the protein concentration therefore, not applicable to all the biologics
- High injection volume (~10mL) not ideal for subcutaneous delivery and disables self administration
- Platform ingredients are not GRAS therefore, additional toxicity burden
- Not applicable for ophthalmic administration
- The technology is expensive
- Patent pertaining to Enhanze Technology expiring in 2024 in the EU, 2027 in the US
- Excipients not widely available - potential issue on limited supply of the excipients

Source: Company reports, Secondary Research

Halozyme

Deals and partnership structure

Deal With	Deal For	Upfront ($ mn)	Milestones ($ mn)	Approved Products	Disclosed Pipeline Products
Roche/Genentech	2006– 3 biologics 2018- 3 biologics	20 25	111+ Royalty 495	Herceptin SC (Trastuzumab) Rituxan SC (Rituximab) Phesgo (Petuzumab+Trastuzumab)	Ocrelizumab (phase I) Atezolizumab (phase II)
Baxter international	1 biologic	10	37	Hyqvia (Immune Globulin Infusion 10%) (Takeda)	N/A
Pfizer	6 biologics	8	507	-	N/A
Abbvie	Humira + 9 biologics	23	1,170	-	N/A
Eli-lily	5 biologics	25	800	-	N/A
Bristol Myers	11 biologics	105	1,700	-	Anti CD73 Antibody (phase I)
Alexion	4 biologics	40	640	-	Ravulizumab (phase I)
arGENX	3 biologics	30	500	-	Anti C2 Antibody (Pre-clinical) Efgartigimod (phase III)
Janssen	5 biologics	15	566	Darzalex Faspro (Daratumumab)	N/A

Source: Company reports, MP Analysis

ALTEOGEN Inc.

KOSDAQ: 196170
Market Cap: 4.85 T KRW ($ 4.1 B)

Alteogen is a South Korea-based biopharma company established in 2008

Hybrozyme Technology:

Alteogen's technology uses Human Hylauronidase (PH20) to enable subcutaneous injection. Their PH20 variant substitutes amino acid residue in wild-type PH20 with another residue having a similar side chain like lysine, arginine and histadine. This increases enzymatic activity and thermal stability of human hyaluronidase PH20.

Advantages:

- Their PH20 variant demonstrated increased protein expression levels and increase in protein aggregation temperature in CHO cells as compared to wild-type PH20 – the PH20 variant can be efficiently produced while having high thermal stability
- PH20 variant showed lower activation level of CD4+ and CD8+ T cells as compared to PH20 – lower possibility of triggering an immune response than wild-type PH20

Disadvantages:

- Similar to Halozyme

Pipeline: Alteogen has a Herceptin SC formulation in early development. They have multiple molecule deals with pharmaceutical companies:

Deal With	Deal For	Upfront ($ mn)	Milestones ($ mn)
Undisclosed	Multiple subcutaneous biologics	13	1373
Undisclosed	Multiple products	16	3870

Source: Company reports, Secondary Research

Viscosity Reducing Technologies

Bhami Research Lab (BRL) was founded in 2014 and is based out of Mangalore, India

BRL's High Concentration Protein Formulation Technology (HiC):

- BRL uses GRAS category excipients, nicotinic acid and tryptophan, as viscosity reducing agents in high concentration protein formulations
- These excipients already used in high amounts as nutritional formulations, with no toxicity concerns
- The combined amount of excipients used in BRL's formulation is <20 mg/mL

MAbs	Formulation Characterization Studies To Date									
	Innovator Conc. (mg/ml)	Max. Conc. at 20-25 cP (mg/ml)	Viscosity	Protein Structure	Stability	Biochemical Activity	MAb Binding Kinetics	Effect of plasma osmolarity	In vivo PK/Tox – IV vs. SC	Syringe ability
HGG		250	√	√	√ (40°C for 14 days)	√		√		√
Bevacizumab	25	263	√	√						√
Trastuzumab	21	264	√	√	√ (4,25 and 40°C for 180 days)	√	√		√	√
Rituximab	10	225	√	√						√
Cetuximab	2	200	√	√						√
Etanercept	2	200	√	√						√
Infliximab	10	250	√							√

Advantages and Challenges with the BRL Technology

Advantages:

- BRL technology is applicable to a wide range of proteins/mAbs
- The technology offers protein concentrations >250 mg/ml; viscosity between 20-25 Cp enabling injection even through 29G needle
- Stable at 4 °C, 25 °C and 40 °C; no signs of aggregation (6 months stability data available)
- All reagents belong to 'Generally Recognized as Safe' (GRAS) category hence no toxicity studies related to the technology needed
- The excipient combination doesn't contain arginine and is appropriate for ophthalmic formulations
- Technology has been validated by one of the top 5 MNCs
    - Several partnership dialogs already underway

Challenges:

- Excipients haven't been used in commercially available protein formulations/in clinical trials yet
- Since the BRL technology is limited by volume, more than one injections may be needed to fulfill dosing requirement for very high dose biologics

ReForm BIOLOGICS

ReForm Biologics LLC, based out of Massachusetts, United States, was founded in 2014

Technology:

Reform biologics uses viscosity reducing excipients to formulate stable, high concentration biologics to enable subcutaneous injection/device assisted administration.

- The primary excipient used is Caffeine. Other excipients used for viscosity reduction are hindered amines, aromatics, functionalized amino acids, oligopeptides, short-chain organic acids, low-molecular-weight aliphatic polyacids, and diones and sulfones

Studies:

Protein	Originator Concentration(mg/mL)	Excipients	Final Conc. (mg/mL)	Viscosity (cP)
Trastuzumab	21	Caffeine (10 mg/mL), Salicylic acid (10 mg/mL)	244	9.7
Bevacizumab	25	Caffeine (10 mg/mL)	213	22
Adalimumab	50	Caffeine (15 mg/mL), Histidine (3 mg/mL)	244	20

Advantages:

- Their excipients eliminate the need for surfactants thereby avoiding degradation

Disadvantages:

- Excipients to be tested and chosen from a pre-identified list – one combination doesn't suit all the formulations
- Caffeine is not a GRAS category excipient hence, there are safety concerns with the technology
- Toxicity was observed at > 50 mg/L of blood
- Not applicable for ophthalmic administration as arginine may be used in combination with Caffeine as a viscosity reducing agent

Source: Company reports

ReForm BIOLOGICS

Deals and partnership structure

Reform biologics has multiple deals with pharmaceutical companies however, they haven't disclosed the products included in the deal or the deal value

Deal With	Deal Type	Deal For
MilliporeSigma	Global license agreement and collaboration	MilliporeSigma will fund R&D and manufacture and commercialize ReForm Biologics' excipients to MilliporeSigma's customers
Bayer AG	Feasibility study	2 clinical stage products
Astellas Pharma	Collaboration	A clinical stage biologic, Astellas will provide funding
KBI Biopharma	Equity Investment & Collaboration	Collaboration to help customers extend product lifecycles, enable improved dosing for patients, and enhance manufacturing efficiency

Source: Company reports, Secondary Research

ExcelseBio

Excelse Bio, based in California, United States, is an affiliate of Integrity Bio, Inc. and was founded in 2014.

Technology:

- Use of amino acids in protein formulations permits retaining viscoelastic properties found in dilute solution without modifying the protein structure
- Excelse Bio uses a proprietary blend of amino acids to coat viscosity causing regions of the molecule, allowing them to be concentrated together while limiting the risk of aggregation and instability
- Excelse uses Proline or Glycine for reducing viscosity, and amino acid for stability is selected from Glycine, Serine, Threonine, Alanine, Arginine, Methionine, Lysine, Proline, Asparagine.

Protein	Originator Conc. (mg/mL)	Excipients (concentration in w/v %)	Final Conc. (mg/mL)	Viscosity (cP)	Stability
Infliximab	10	Proline+Glycine (10%)	150	17	3 days at 45°C
Trastuzumab	21	Proline+Glycine (10%)	200	30	20 hours at 55°C
Rituximab	10	Serine + Proline (10%)	200	12	20 hours at 55°C
Palivizumab	100	Serine + Proline (5%)	250	N/A	N/A

Advantages:

- Effective viscosity reduction up to 250 mg/mL

Challenges:

- Excipients to be tested and chosen from a pre-identified list – one combination doesn't suit all the formulations
- Long-term stability data not available

Source: Company reports

ExcelseBio

Deals and partnership structure

Pipeline:

Formulations with trastuzumab, rituximab and infliximab in development.

Partnerships:

Excelse Bio has partnerships with 2 companies for un-disclosed biologics and they have successfully completed a feasibility study.

However, over the last 5 years, there and there are no updates on partnered molecules, suggesting no successful outcomes yet.

Source: Company reports, Secondary Research

Arecor

Arecor, based out of UK, was spun out of Unilever Research in 2007.

Technology:

Arecor has >10 unique platforms to enable high concentration protein formulations. Arestat Technology uses buffering agents and excipients for stability and low viscosity.

- An oligomer of ethyleneimine at a concentration of about 0.2 mg/mL to about 5 mg/mL is used to address the problem of aggregation, reducing viscosity and reducing undesired fragmentation of antibody proteins at high concentrations
- Arecor formulated Rituximab at a concentration of 140 mg/mL in EDTA (0.2 mM), methionine (1 enehexamine Ethanol) and non-pegylated oligomers of ethyleneimine and demonstrated reduction in aggregation
- Arecor has also demonstrated reduced aggregation in Certolizumab Pegol at 100 mg/mL (originator concentration is 200 mg/mL)

Advantages:

- Effective reduction in aggregation

Challenges:

- Various oligomers (pegylated and non-pegylated) are tested to achieve the desired formulation properties – one combination of excipients doesn't suit all formulations
- Concentrations demonstrated with Rituximab and Certolizumab Pegol still low as compared to other technologies
- The size of ethyleneimine oligomer or polymer is directly related to the cytotoxic effect
- Arginine may be used as a tonicity modifier in some formulations limiting the use of this technology in ophthalmology

Source: Company reports, Secondary Research

Arecor

Landmark Deals and partnership structure

Pipeline:

Arecor has Ultra-Concentrated Rapid Acting Insulin in pipeline in phase I study for Diabetes. This product has the potential to provide the benefits of a rapid acting insulin to patients who have high daily insulin requirements via a single injection and enable the use of miniaturized delivery devices to improve patient compliance.

Partnerships:

Partnered With	Deal Type	Deal For	Deal Value ($ mn)	Disclosed Pipeline Products
Hikma Pharmaceuticals	Co-development	Small molecule	Upfront +Milestone	N/A
GlaxoSmithKline	Technology licensing	Vaccines	N/A	N/A
JDRF	Research, Development and Commercialization agreement	Insulin	Contribute matching funds	liquid coformulation of pramlintide and insulin

Arecor, along with the partnerships mentioned above, has a few undisclosed partnerships for development of differentiated biosimilars as well as innovative products.

Source: Company reports, MP Analysis

Arsia Therapeutics, based in Massachusetts, United States, was founded in 2013, was acquired by Eagle Pharmaceuticals in 2016.

Technology:

- Arsia Therapeutics uses hydrophobic bulky polar organic compounds to develop high concentration subcutaneous dose forms for therapeutic proteins for convenient administration
- Some of the camphorsulfonic acid derivates used in high concentration formulations are: camphorsulfonic acid lysine (CSAL), camphorsulfonic acid arginine (CSAA), benzenesulfonic acid lysine (BSAL), benzenesulfonic acid arginine (BSAA), naphthalenesulfonic acid arginine (NSAA), and camphorsulfonic acid l-(3-aminopropyl)-2-methyllH-imidazole (CSAAPMI)

Protein	Original Conc. (mg/mL)	Excipients	Final Conc. (mg/mL)	Viscosity (cP)
Infliximab	10	CSAA	215	54
Cetuximab	2	CSAAPMI	226	26
Bevacizumab	25	CSAAPMI	210	41
Etanercept	50	Thiamine HCl	212	141
Trastuzumab	21	CSAA	216	56
Rituximab	10	CSAAPMI	202	39

Disadvantages:

- Excipients to be tested and chosen from a pre-identified list – one combination doesn't suit all the formulations
- Not applicable for ophthalmic use
- Potential toxicity associated with camphor sulfonic acid; limited evidence available yet

Source: Company reports, MP Analysis

Landmark Deals and partnership structure

Partnerships:

Arsia had several early stage partnerships with pharmaceutical companies apart from the disclosed partnership with Biogen.

Deal With	Deal Type	Deal For	Deal Value ($ mn)	Disclosed Pipeline Products
Biogen	Collaboration	Formulations for Hemophilia research	Upfront + up to $100 M milestone payment	-
Eagle Pharmaceuticals	Acquisition	To expand formulation and development expertise in biosimilars	$30 M + up to $48 M milestone payment	-

Arsia was acquired by Eagle Pharmaceuticals in 2016 and Eagle's pipeline is primarily focused on small molecules.

Source: Company reports, Secondary research

Comparison Of Formulation Technologies

BRL's technology demonstrates superior viscosity reduction as compared to the competitors

Molecules	Bhami Research Lab		Reform Biologics		Excelse Bio		Arecor		Arsia Therapeutics	
	Conc.	Viscosity	Conc.	Viscosity	Conc.	Viscosity	Conc.	Viscosity	Conc.	Viscosity
Bevacizumab	263	20	213	22	-	-	-	-	210	41
Trastuzumab	275	19	244	10	200	30	-	-	216	56
Rituximab	225	22	-	-	200	12	140	-	202	39
Cetuximab	200	21	-	-	-	-	-	-	226	26
Etanercept	200	15	-	-	-	-	-	-	212	141
Infliximab	250	20	-	-	150	17	-	-	215	54

Although there are a few technologies offering viscosity reduction at high concentrations of proteins, BRL has a standardized protocol and uses the same set of excipients to addresses formulation challenges for a wide range of proteins.

BRL's technology offers concentrations >200 mg/mL at viscosities ~20 cP. Additionally, BRL's GRAS category excipients eliminate the safety concerns and can potentially be used in Ophthalmology.

Source: Company reports, MP Analysis

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