Proteins and peptides are an important class of drugs as they allow for better treatment of many diseases by having higher specificity and activity. However, many biotherapeutics face numerous formulation hurdles such as poor stability, aggregation, and short half-life, which may in turn cause such promising molecules to be shelved. Alternatively, if developed, they may have limited commercial attractiveness due to sub-optimal safety, efficacy, or convenience. In addition, development and manufacturing costs associated with this class of drugs are significantly higher than those of small molecules.

The use of traditional sustained-release systems for proteins and peptides can solve some of these problems but also creates a number of challenges. These include: complexity of formulation processes under aseptic conditions; stability of the drug, especially when organic solvents are involved; burst effect; local tolerability; and low bioavailability. The use of polymeric systems, such as PLA/PLGA, has been studied for more than 25 years but still requires the use of organic solvents and is therefore not adapted to large and fragile protein formulation.

Other approaches used to prolong the half-life of biologics, such as protein engineering (for example, PEGylation, albumin fusion and
Fc fusion) necessitate the development of a new biological entity (associated with higher clinical development risks and costs) and generate drastic decrease of the biological activity due to detrimental conjugation and/or steric hindrance issues.

The Medusa® drug delivery platform has been designed to address the challenges related to the formulation, pharmacokinetics and safety profile of biologics. Medusa enables the creation of precise pharmacokinetics of biotherapeutics over time, leading to a reduction of side-effects and better treatment compliance.

The amphiphilic Medusa polymer is based on a hydrophilic biodegradable polyglutamate chain grafted with hydrophobic Vitamin E. The polymer self-assembles in aqueous medium to form a stable solution of nano-sized hydrogels comprising multiple polymer chains and 95% water. The hydrogel is formed by hydrophobic interactions only, no chemical cross linking agent is required. A diagrammatic overview of how the polymer chain and the drug self-assemble in water to give the hydrogel, and the resulting PK profile after administration, is given in Figure 1.

Formulated with Medusa, the biological entity will spontaneously associate with the hydrogel through reversible hydrophobic and/or electrostatic interactions (Figure 2). The solution containing non-covalently bound hydrogel/biologics complexes is ready to be administered.

Based on hydrophobic and/or electrostatic interactions, this association step is performed conveniently in water at room temperature, without the use of any organic solvents, heat or shear mixing. The liquid formulation containing the hydrogel can be sterile filtered, then filled in vials or cartridges or freeze-dried and reconstituted in water.

The scale-up and transfer of the formulation process are easy and do not require sophisticated handling or reactors (see Figure 3). The mild conditions used allow the proteins or peptides to maintain their complete structural and functional integritys, as proved by a panel of analytical methods such as RP-HPLC, SEC, Western Blot and bioactivity studies following extraction from the Medusa hydrogel.

After subcutaneous injection, a depot is formed at the injection site and the fully active biologic is slowly released in vivo over one to fourteen days in humans, as it is displaced by competition with physiological proteins (such as human serum albumin) available in high concentrations in the subcutaneous tissue.

By adjusting the hydrogel/biologic ratio, the length of the polyglutamate chain, and the amount of Vitamin E, the association of the formulated biologic with the polymer can be finely tuned, and so accommodate any physicochemical and structural features of most biologics, best adapted to the therapeutic objective.1

As an example, interferon alfa-2b (IFN-α-2b) has been formulated with Medusa to extend the release over one week in humans, and is currently in a Phase II clinical study in France (ANRS HC 23 COAT-IFN).2

In vitro, it has been demonstrated that using serum bovine albumin (BSA), the interferon is released upon increasing albumin concentration (Figure 4), and that the interferon is chemically unchanged as evidenced by RP-HPLC. The release is complete with excess BSA and, when tested for in vitro activity, 100% activity is observed. Indeed, the Medusa/interferon association is physical in nature and fully reversible, enabling the controlled delivery of non-denatured, fully-active proteins within the appropriate therapeutic window.

In summary, Medusa is well suited to meet challenges in developing and manufacturing formulation of biologics. It allows not only the sustained delivery of biological drugs, from one day to up to two weeks in humans, but also the solubilisation of poorly soluble molecules (for example, solubilisation of IL-2 (Proleukin®), which has been enhanced by 35 times using Medusa). Improvement of the safety profile is also achieved. Since no chemical modification is required, the application of Medusa to the lifecycle management of existing biological drugs is straightforward from a clinical and regulatory point of view.

**BENEFITS OF MEDUSA**

The advantages of Medusa over other drug delivery systems are summarised in Figure 5.

The key benefits of Medusa include:
- Applicable to a wide range of peptide and protein drugs as well as small molecules
- Sustained delivery from 1 to 14 days in humans
- Combination of different drugs in the same formulation
- Remarkable increase of solubility of poorly soluble biologics
- Full activity of biologics maintained
- Improved safety profile / good local tolerance
- Safe, non-immunogenic, fully biocompatible and biodegradable hydrogels: glutamatic acid and Vitamin E are GRAS
- GMP manufacturing of the polymer at commercial scale
- Bio-friendly, water-based process
- Formulation process is cost effective, easy to implement, to scale-up and to transfer
- Strong intellectual property position and freedom to operate (no third party licensing obligations).

---

**Figure 3: A “Bio-Friendly”, Rapid and Easy-to-Scale-Up Formulation Process.**

**Figure 2: Efficient Loading of Various Proteins (with no Sequence/Structural Similarities).**

**Table 1: Medusa Hydrogel (95% water) pH, salt adjusted.**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Loading wt/wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>hGH</td>
<td>80%</td>
</tr>
<tr>
<td>IFN-α-2b</td>
<td>100%</td>
</tr>
<tr>
<td>EPO</td>
<td>200%</td>
</tr>
<tr>
<td>BSA</td>
<td>&gt;250%</td>
</tr>
</tbody>
</table>

**Figure 4:**

Capillary Electrophoresis

Medusa: 0.1 mg/ml

Protein: 0 to 0.5 mg/ml

Phosphate buffer

Max. Loading wt/wt
Flamel Technologies SA (NASDAQ: FLML) is a leading drug delivery company dedicated to develop safer, more efficacious formulations of drugs addressing unmet medical needs. Its product development pipeline includes biological and chemical drugs formulated with the Medusa® and Micropump® proprietary platforms.

The Medusa platform (injectable drugs, described here) for the formulation and/or the extended release of biologics (including proteins, antibodies, and peptides) as well as small molecules.

• DeliVax™, Medusa’s vaccine application, permits the efficient formulation of antigens.

The Micropump micro-encapsulation platform (oral drugs) for the formulation and the controlled release of chemical drugs, is designed to increase the absorption time of drugs, particularly for drugs only absorbed in the small intestine and to deliver the drug in specific sites in the gastro intestinal tract. Micropump allows tailoring the exact kinetics required to optimize the final product and offers the advantage to easily and accurately mix microparticles with different release kinetics, in different ratios, every single particles performing independently. Micropump can be presented in various dosage forms such as capsule, tablet, sachet or oral suspensions (LiquiTime™) without modifying the release rate.

The company’s has developed products approved in the USA and in Europe and manufacture Micropump-based microparticles.

• LiquiTime™, allowing stable and controlled release ready-to-use liquid oral suspensions of one or several combined drugs over time.3

• Trigger Lock™ for the controlled release of narcotic and opioid analgesics while deterring tampering (particles cannot be crushed to extract the active).

These versatile drug delivery platforms may be used to address threshold formulation problems such as poor solubility, aggregation and instability for both chemical and biological drugs. The company’s innovative delivery platforms are used for the LCM of marketed products, including Biobetters, and the development of new compounds with many unique competitive advantages:

• Improvement of drug characteristics such as efficacy, bioavailability and pharmacokinetics

• Improvement of the drug safety profile with a noticeable diminution of peak dose concentrations, which in turn allows administration of higher effective doses and potentially greater efficacy

• Potential improvement of patient compliance due to reduced side-effects and greater convenience

• Protection of market position through patent extension and/or product differentiation

• Extension of market to new indications and new patient populations.

Flamel Technologies has collaborations with a number of leading pharmaceutical and biotechnology companies, including Baxter, GlaxoSmithKline (Coreg CR®, carvedilol phosphate), Merck Serono and Pfizer.

Medusa® and Micropump® are registered trademarks of Flamel Technologies SA.

REFERENCES:

1. US DMF Type IV on Medusa Polymer (filed: assigned number 024634).

www.ondrugdelivery.com

Copyright © 2011 Frederick Furness Publishing

Figure 4: Non-covalent Association and Total Release from Medusa Hydrogel.

Figure 5: Key Advantages of Medusa Over Other Drug Delivery Approaches.