A hydrogel depot formulation platform is well suited to the formulation of biobetter products – both original biologics and biosimilars – as no chemical modification is required and so development is relatively straightforward from a clinical and regulatory perspective.

‘biobetter’, it is perhaps best defined as a “biological that has been structurally and/or functionally altered to achieve an improved or different clinical performance” (2).

While biosimilars are simply copies of first-generation products, ‘biobetters’ are designed to offer benefits over such products, giving the opportunity to compete with innovator molecules from an efficacy, safety and patient compliance point of view. Indeed, a biobetter product can modify key properties of an original drug, without fundamentally changing its mechanism of action. Examples include:

- Increasing the resident exposure or bioavailability
- Prolonging the circulating half life or the Tmax pharmacokinetic parameter
- Reducing the incidence of side effects via reduction of the Cmax pharmacokinetic parameter, while staying within the therapeutic window
- Changing the route of administration (for example, from intravenous to subcutaneous)

Biobetter Development Strategies
Currently, there are two main approaches to developing biobetters and improving the properties of marketed biologics (see Figure 1). The first is protein engineering or chemical modification, and the second is use of a non-modifying formulation.

Although these two strategies rely on the same regulatory and safety data of marketed drugs, they require a priori different development paths. Notably, the non-modifying formulation approach involves a reduction in time to market and associated costs, as compared with the protein engineering or chemical modification approach.

Biobetters obtained through protein engineering or chemical modification lead to the creation of new biological entities (NBEs); these require as much preclinical work (especially toxicity studies) and clinical research as the original molecule, and consequently they lose the advantages of the abbreviated regulatory route for biosimilars (for example, 505(b)2 in the US). While the risk of failure is expected to be somewhat lower than with most NBEs, it is still likely to be higher than with a conventional biosimilar product. This was the case, for example, with Albuferon, a longer-acting form of Roche’s recombinant interferon alpha under development by Human Genome Sciences; despite having a lower dosing frequency, the drug was associated with adverse pulmonary events in Phase 3 trials and subsequently withdrawn from development.

A Non-Modifying Drug Delivery Platform
At Flamel, we have developed a non-modifying drug delivery hydrogel, Medusa (3), that enables the development of improved versions of biologics that do not...
modify or denature the original drug, and can therefore benefit from shorter development and regulatory pathways, in much the same way as biosimilars.

Medusa-based formulation of validated drugs offers a lower-risk strategy for the development of biobetters, offering:

- Improvement of drug characteristics, such as efficacy and pharmacokinetic parameters
- Improvement of the drug safety profile with a noticeable diminution of peak dose concentrations, as well as peak-through ratio which in turn enables administration of higher effective doses and thus potentially greater efficacy
- Potential improvement in patient compliance due to a reduced incidence of side effects and greater convenience
- Life cycle management through patent extension and/or product differentiation
- Extension of opportunity to new indications and patient populations

The development risks are expected to be somewhat comparable to those for biosimilars but are lower than with NBEs, including those generated using protein engineering or chemical modification.

Since no modification of the biotherapeutic is involved, the non-clinical development of Medusa-based biobetters cross-references the original safety dosiers of the biotherapeutic and the Medusa polymer; consequently only a few bridging, non-clinical studies between the two dosiers are required. In addition, clinical development plans are usually greatly reduced.

The Medusa polymer is considered to be an excipient by the regulatory agencies (EMA and FDA), and has well-defined and documented pharmacology and toxicology characteristics. Indeed, a complete non-clinical ADME and regulatory toxicology package for the polymer has been filed with the FDA (Type IV US-DMF; assigned number: 024634).

This drug master file (DMF) contains data pertaining to safety pharmacology, immunotoxicity, genotoxicity, reprotoxicity, local tolerance and repeated dose up to six months.

**Conclusion**

A hydrogel depot formulation platform (Medusa) has been found to be well suited to meet the challenges encountered when developing biobetter products. It enables the non-modifying formulation of better biotherapeutics (whether comprising original biologics or biosimilars). In addition, it permits the sustained delivery of a biotherapeutic – from one day to two weeks in humans – and also facilitates the solubilisation of poorly soluble molecules (4) and improvement of their safety profile.

As no chemical modification is required, use of the formulation technology for life cycle management of existing biotherapeutics (including proteins and peptides) – and also small molecule drugs – is relatively straightforward from a clinical and regulatory development point of view.

**Note:**

Medusa is a registered trademark of Flamel Technologies SA.

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**References**

4. The solubilisation of IL-2 (Proleukin®) has been enhanced by 35 times using Medusa