drug. First, the reference product formulation may be protected under a patent; as the composition patents for biological drugs have come off patent, the originators have embarked on an aggressive strategy to patent all other components of the product, including the formulations; although many of these patents will eventually be challenged and in all likelihood be taken down, the biosimilar developer faces a choice, when sharing its dossier with the originator, how far to go to obviate any IP, regardless of this robustness. In other instances, the formulation change may be required to improve the product. An interesting example is that of Humira.

> The current commercial formulation of HUMIRA (each 0.8 mL) contains adalimumab 40 mg, citric acid monohydrate 1.04 mg, dibasic sodium phosphate dihydrate 1.22 mg, mannitol 9.6 mg, monobasic sodium phosphate dihydrate 0.69 mg, polysorbate 80 0.8 mg, sodium chloride 4.93 mg, sodium citrate 0.24 mg and Water for Injection, USP. Sodium hydroxide is added as necessary to adjust pH.

The PCT/US2013/0586181 (Coherus) provides a claim that states:

> An aqueous, buffered pharmaceutical composition comprising adalimumab and a buffer, wherein (i) the composition is free or substantially free of a buffer combination that comprises both a citrate buffer and a phosphate buffer; and (ii) the composition exhibits long-term stability. So if both citrate and phosphate are used then, this IP does not apply.

Citrate is well known to cause significant discomfort and as a result, Humira has been proposed to be reformulated as a high-concentration buffer-free formulation, for which a new patent (8,821,865) has been issued claiming the following:

A liquid aqueous formulation comprising:

> (1) 100 mg/mL of adalimumab; (2) 1.0 mg/mL of polysorbate 80; and (3) 42 mg/mL of mannitol; wherein the formulation has a pH of 4.7 to 5.7 and does not contain a buffer or a salt, and wherein injection of the formulation into a human subject results in a Pain Visual Analog Scale (VAS) score of less than 1.0.

Obviously, the issue of discomfort using citrate was well known to the originator, but the change is proposed only when the composition patent is about to expire—this will not keep the competition out but provide the originator an opportunity to differentiate their product as safer. Whether these considerations borderline on ethical grounds or not remains to be seen.

U.S. Patent 8,795,670 states:

> A stable liquid aqueous pharmaceutical formulation comprising (a) a human IgG1 anti-human Tumor Necrosis Factor alpha (TNFα) antibody, or an antigen-binding portion thereof, at a concentration of 45 to 105 mg/mL,