the product is similar to fingerprint-like comparisons, no further studies may be required if the similarity data removes residual uncertainty.

It is important, therefore, to understand what constitutes residual uncertainty. As discussed earlier, any uncertain or unexpected observation about the product creates a residual or remaining uncertainty. Note that it is not the uncertainty or the unexpected observations but that these remain uncertain is the focus of description. For example, if the biosimilar candidate shows extra chromatography peaks that are fully identified and are established to not impact the structure of the protein at any level, then these do not remain residually uncertain.

4.6 Fingerprint similarity

The regulatory guidance provided by the FDA has always been evolutionary and in some instances revolutionary—in the case of biosimilars, it is the latter; the concept of biosimilarity is based on the scientific rationale that has evolved, yet still questioned by many. A good example of how the FDA, unlike any other regulatory agency in the world, takes a bold step is exemplified by the example of the approval of low–molecular weight heparin (LMWH). The product was approved without any phase 3 clinical trials, despite the hue and cry by the originator of the product (meaning several citizens' petitions, extensive press coverage to clinicians to confuse the science, and commercial efforts to protect a multibillion dollar franchise).

The FDA stated that

> the EMA has set guidelines for LMWH products such as enoxaparin that only require the products to contain a similar (as opposed to the same) active ingredient to that contained in another already marketed LMWH product. Because the proposed LMWH product in Europe will contain an active ingredient that is similar to (as opposed to the same as) the brand name product, there might be uncertainties as to whether the two products are the same with regard to safety and effectiveness. Thus, sponsors of a similar enoxaparin product under the EMA framework are expected to provide clinical studies showing comparable effectiveness to the proposed similar LMWH product as well as clinical data showing comparable safety (including with respect to Heparin Induced Thrombocytopenia).
>
> In contrast, the FDA requires a generic enoxaparin product to contain the same active ingredient as Lovenox. Based on the FDA's scientific experience and expertise, and relevant scientific information, the FDA has concluded that the five criteria (see response to Q#8) are sufficient to ensure that the generic enoxaparin product has the same active ingredient as Lovenox. The FDA also evaluates impurities in the generic enoxaparin product, particularly with respect to their effect on immunogenicity. With the FDA approach, there is no scientific need to perform additional clinical studies to demonstrate equivalence of clinical effectiveness and