Table 2 Studies needed to support changes in formulation during early clinical trials

Research requirements	Supporting results
Purity	Stability, compatibility, structural analyses
Potency	In vitro/in vivo bioassays, preclinical, and/or clinical pharmacokinetic comparability
Safety	Preclinical safety

schedules, are scaled up and poised for pivotal trials. As many other changes relevant to the chemistry, manufacturing, and controls (CMC) package are occurring at this time, it is the most efficient time to incorporate any formulation changes to the final campaign to demonstrate the commercial feasibility of the product.

Since a formulation change can potentially introduce substantial adverse effects on the purity or potency as related to the safety or effectiveness of the product, solid justifications are required for any proposed changes. These justifications must be based on relevant methods and results to evaluate the effect of the change as related to the product's safety or effectiveness (Appendix Regulatory Documents 18–20). Although changes in degradation profiles after formulation modifications are undesirable, if the degradation profile changes qualitatively or quantitatively it is recommended to follow the impurity-related guidelines (Appendix Regulatory Documents 2,3).

Assuming that the formulation change does not affect the route of administration, pharmacokinetic, or pharmacodynamic properties of the product, additional purity, potency, and safety studies (Table 2) should be conducted. Also, results from real-time stability at the recommended storage condition are required to establish an expiry date. However, comparable stability between the old and new formulations can be demonstrated based on results from accelerated stability studies. This will require both good stability data from the old formulation, including both an accelerated stability study and a real-time stability study, as well as a good understanding of how degradations observed from accelerated stability studies can be safely extrapolated to recommended storage conditions.

Switching formulations after reaching the market will require a formal submission and approval of amendments to regulatory agencies. As a part of this process, clinical studies to demonstrate the comparable safety and efficacy of the product will be required, which will involve human pharmacokinetic comparability studies in addition to all the studies listed in Table 2.

Strategy for Different Modality of Biologics

While general approaches in formulation optimization and processes for various biologics should be similar, different characteristics of individual modalities require different formulation attributes. These differences appear to be consistent among commercialized products, so general strategies applied for different modalities can