Since the introduction of Hatch-Waxman Act in 1984, literally thousands of products have been approved as generic products. This has served well for the availability and affordability of numerous immediate release and some modified release products to the needy patient population. The important elements of 505j or ANDA applications are the demonstration of “pharmaceutical equivalence” and then “bioequivalence” of the test product as compared to their brand or RLD formulations. A demonstration of pharmaceutical and bioequivalence implies therapeutics equivalence. A review of approved brand products would indicate that there are still several off-patented RLD products for which there are no approved generics. In the 21st century, there is a growing list of extremely complex products for which the traditional paradigm of pharmaceutical and bioequivalence is fraught with challenges. It is important that the scientific community across the globe become aware of it and work together to resolve the complicated issues of making the drug products available to patients when they need it. This presentation will highlight the challenges of bioavailability and bioequivalence of complex products in the 21st century.