potential routes of administration include suppository or buccal methods involving fast-dissolving minitablets or strips that are placed in the mouth. Although these appear to be attractive options for older infants above 6 months, they have not been explored for neonates.

Even after all the challenges cited above have been negotiated, there are considerable challenges in clinical trial design and demonstration of clinical efficacy for registration. Some of these factors are expanded upon in more detail in the last section of this chapter, but in brief, for adults the main challenges are enrolment of trials to power endpoints and virus detection and diagnostics. Immunosuppressed patients are too few to enroll and power trials easily. Elderly patients with underlying conditions such as COPD are more abundant, but the low level of virus that is typical in these subjects can be difficult to detect. In contrast, all infants by the age of 2 years will have an RSV infection and typically have high viral loads that can be readily detected, thus obviating the diagnostic issue. However, trials in infants require consent from guardians and carry an ethical hurdle in that demonstration of efficacy and safety in other patient groups, *i.e.* adults, is likely required prior to infant trials in order to justify the risk-to-benefit factor.

A final challenge of note clinically is understanding the timing of intervention in the disease. Ideally, any treatment option, regardless of mechanism, is most effective when given as early as possible in the disease course. However, this is not always feasible and it is anticipated that infection would have progressed for several days before symptoms are severe enough that patients or caregivers would seek medical attention. Most importantly, the disease begins in the upper respiratory tract and then progresses to the lower respiratory tract, where the greatest risk and highest morbidity occur. Intervening before lower respiratory tract infection is preferred. Although this logically applies to all RSV inhibitors regardless of mechanism, it is perhaps most relevant for a fusion inhibitor, which by virtue of mechanism is designed to prevent virus spread to uninfected cells. If widespread infection in the upper respiratory tract has occurred, it is unlikely that a significant impact can be made on virus in this cavity. Similarly, for the lower respiratory tract infections, if intervention is too late then minimal benefit may be anticipated for a drug that blocks new infection. In contrast, replication inhibitors might still impact virus production in infected cells in both the upper and lower respiratory tract. It is reasonable on this basis to suggest that fusion inhibitors will be particularly sensitive to the timing of intervention in the disease course. Therefore, the challenge for drug developers of fusion inhibitors would be early detection and early treatment, with early diagnosis of RSV critical. There are several options for the detection of RSV: cell culture, antigen-based tests and PCR, with RT-PCR being the most rapid detection system. Antigen-based tests also offer rapid detection, but lack specificity. Multiplexing several rapid detection systems such as RSV, human metapneumovirus and influenza A and B would be highly desirable, since co-infections often exist and RSV infections could be misdiagnosed as influenza.[25]

Overall, the challenges associated with the development of RSV fusion inhibitors span the whole development process and present a significant hurdle.