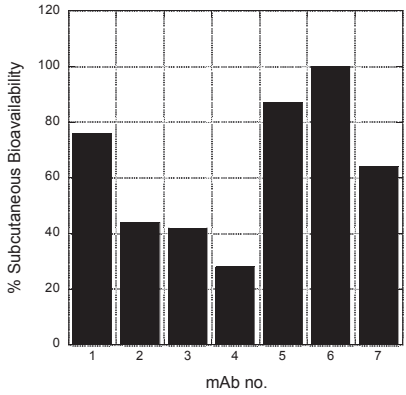

Figure 6.4 Bioavailability of seven different mAbs after subcutaneous delivery.
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of the pumps resulting in a decrease of membrane flux requiring very long times to reach the targeted concentration. Higher viscosity of mAb solutions also may make it difficult to recover the concentrated solution resulting in economically unacceptable losses (Shire, 2009; Shire, Shahrokh, & Liu, 2004).

Bioavailability of a high-concentration mAb formulation for SC delivery

The bioavailability of mAbs given by the SC route of administration can vary widely. In a study using a minipig model, it was shown that the bioavailability of seven mAbs ranges from 24% to 100% (Figure 6.4). Several factors have been cited that govern the bioavailability of proteins administered SC and include the role of the lymph and blood capillaries in systemic absorption: the site of the SC injection, variability between patients related to the SC layer morphology, the depth of the injections, molecular properties of the mAbs, stability of the mAbs, and mAb formulation. The major focus for pharmaceutical development is stability and formulation of the mAbs. Recent studies suggest that positively charged mAbs may bind to SC tissue depending on the ionic strength and pH of the mAb formulation (Mach et al., 2011). The impact of this binding can be modulated by increasing formulation ionic strength or by increasing the mAb concentration resulting in a saturation of the binding to the tissue. The effect of increasing the formulation ionic strength was demonstrated using an ex vivo rat model. Specifically, two mAbs were incubated with rat SC tissue using formulations with different ionic strengths and the amount of mAb not absorbed to tissue was determined using size exclusion chromatography (SEC) of the supernatant after centrifugation to remove cell debris. An increase in the formulation ionic strength resulted in a decrease of mAb bound to SC tissue suggesting an electrostatic mechanism. The impact of multiple charged buffer species was also investigated and it was shown that specific binding of these charged species may alter the electrostatic