The TNF family member protein BAFF/BLyS is essential for B cell survival and plays an important role in regulating class switch recombination as well as in the selection of autoreactive B cells. In humans, increased concentrations of soluble BAFF are found in different pathological conditions, which may be as diverse as autoimmune diseases, B cell malignancies, and primary Ab deficiencies (PAD). Because the mechanisms that regulate BAFF levels are not well understood, we newly developed a set of mAbs against human BAFF to study the parameters that determine the concentrations of soluble BAFF in circulation. Patients with PAD, including severe functional B cell defects such as BTK, BAFF-R, or TACI deficiency, were found to have higher BAFF levels than asplenic individuals, patients after anti-CD20 B cell depletion, chronic lymphocytic leukemia patients, or healthy donors. In a comparable manner, mice constitutively expressing human BAFF were found to have higher concentrations of BAFF in the absence than in the presence of B cells. Therefore, our data strongly suggest that BAFF steady-state concentrations mainly depend on the number of B cells as well as on the expression of BAFF-binding receptors. Because most patients with PAD have high levels of circulating BAFF, the increase in BAFF concentrations cannot compensate defects in B cell development and function.