The 33rd Infantry was activated on 6 July 1916 in accordance with War Department General Orders Number 22 dated 30 June 1916 that ordered seven new regiments to be organised; four in the Continental United States, one in the Philippine Islands (31st Infantry Regiment (United States), one in Hawaii (32nd Infantry Regiment (United States), and one, the 33rd Infantry, in the Canal Zone.[2]

In 1916, when the whole of Europe was engaged in the great war, the United States Congress enacted a law increasing our armed forces. One of the results of this act of congress was the organization of the 33rd infantry which was formed in the Canal Zone July 6, 1916 and has remained on duty here ever since. The enlisted personnel of the regiment was originally drawn from the 5th and 10th infantry stationed at Camps Empire and Otis. During the construction days both camps were occupied by troops after being vacated by civilians. Major General Charles H. Muir was the first regiment commander. Headquarters, machine gun, supply companies, and companies A,B,C,D,E, and F were organized at Camp Empire. Companies G,H,I,J,K,L, and M were organized at Camp Otis. The band section was organized at Fort Jay, N.Y. During the first four years of its existence, the 33rd. infantry was distributed by battalions, and detachments, throughout the canal zone and the Republic of Panama. During the World War, it guarded Gatun Locks, the dam and spillway, the Monte Lirio, and Mindi bridges, the Chagres River bridge at Gamboa. the Pedro Miguel and Mira FLores locks, pier 18 and the dry dock at Balboa. During the period from 1916 to 1920, the regiment was engaged in exploring and charting the jungles of Panama.