Targeted gene integration into site-specific loci can be achieved in Chinese hamster ovary (CHO) cells via CRISPR/Cas9 genome editing technology and the homology-directed repair (HDR) pathway. The low efficiency of HDR often requires antibiotic selection, which limits targeted integration of multiple genes at multiple sites. To improve HDR-mediated targeted integration, while avoiding the use of selection markers, chemical treatment for increased HDR, and fluorescent enrichment of genome-edited cells was assessed in CHO cells. Chemical treatment did not improve HDR-mediated targeted integration. In contrast, fluorescent markers in Cas9 and donor constructs enable FACS enrichment, resulting in a threefold increase in the number of cells with HDR-mediated genome editing. Combined with this enrichment method, large transgenes encoding model proteins (including an antibody) were successfully targeted integrated. This approach provides a simple and fast strategy for targeted generation of stable CHO production cell lines in a rational way.