Cluster-based strategies have been gaining importance in regional and local economic development policy in recent years. This article provides a comparative assessment of cluster initiatives in two medium-sized city regions, Sønderborg in Southern Denmark and Eau Claire in West Central Wisconsin. Despite very different economic settings, both regions face similar economic restructuring challenges as they transition into a more service and IT-based local economy and away from a manufacturing base. We identify cluster-related instruments, compare the policy setup in the two areas, and analyze how they work within the general economic development frameworks of country, state and region. We conclude that in Denmark this cluster approach has brought together more entities resulting in a more comprehensive and better funded policy effort than in Wisconsin.