In a two-chambered osmotic pump system, the drug substance chamber is surrounded by an impermeable membrane with microdrilled orifices. The second chamber, also called the "push chamber" is encapsulated by a semipermeable membrane, and the two chambers are separated by a moveable wall. Water enters the "push chamber" as a result of the difference in osmotic pressure, causing the material in this chamber to expand. This action pushes the moveable wall, which forces drug substance out of the capsule through the microdrilled orifices in the walls of the drug chamber.[34]

There are many other aspects to consider in determining the proper formulation for a clinical candidate that must be finalized before initiating clinical trials. Issues such as hardness, thickness, and friability (the ability of a solid to breakdown into smaller pieces) are unique to oral formulations, whereas issues such as dose uniformity, impurity profiles, and manufacturing methods cut across all types of formulations. Irrespective of the final dosing method and form, decisions on the final drug formulation must be made prior to entering clinical trials.

INVESTIGATIONAL NEW DRUG APPLICATION

Once all of the scientific, manufacturing, and technical hurdles have been overcome, an organization must gain approval before they will be authorized to move forward with human studies. Government agencies such as The Food and Drug Administration (US), the European Medicines Agency (European Union), the Pharmaceuticals and Medical Agency (Japan), and similar agencies across the globe must receive and approve a clinical plan before any potential therapy can be tested in human populations. An Investigational New Drug Application (IND), also referred to as a Clinical Trial Authorization (CTA) or Clinical Trial Notification (CTN), is filed in order to solicit the approval of these agency. The document contains information describing three broad areas of research, (1) Animal pharmacology, safety, and toxicology study data, (2) Chemistry, Manufacturing, and Controls (CMC), and (3) Clinical trial protocols including investigator information.[35]

The animal pharmacology, safety, and toxicology section of an IND describes pharmacological studies that provide proof of efficacy in an accepted animal model of the relevant disease state. This section also includes preclinical safety study data that the regulators will use to determine whether or not the potential new therapeutic agent is safe enough to initiate clinical trials. *In vivo* safety studies from two animal species, one rodent and one non-rodent, run under GLP (Good Laboratory Practices) conditions must also be included. This section also typically includes information derived from many of the safety studies described in Chapter 8 such as Ames testing, micronucleus assay data, chromosomal aberration assessments, and cardiovascular safety assessments. In addition, any data