after noting that this route of injection resulted in systemic absorption. Robert Koch in 1888 developed the first syringe that could be sterilized and Karl Schneider built the first all-glass syringe in 1896. Becton, Dickinson and Company created the first mass-produced disposable glass syringe and needle, developed for Dr. Jonas Salk's mass administration of one million American children with the new Salk polio vaccine.

Like many other critical technologies in sterile product manufacturing (e.g., freeze drying, rubber closures, clean rooms), the sterile, prefilled, disposable syringe was developed during World War II. A precursor to the syringe was the Tubex cartridge system developed by Wyeth (4). The injection solution was filled into a glass cartridge having a needle already permanently attached to the cartridge. The prefilled cartridge was then placed in a stainless steel administration device.

Early practice of administering drugs by injection occurred without knowledge of the need for solution sterility plus no one appreciated what caused pain and local irritation while injecting solutions subcutaneously. It was not until around 1880 when a pharmacist named L. Wolff first recognized the role of isotonicity in minimizing pain and irritation when introducing drug solutions to the body. Intramuscular (IM) injections were first performed by Alfred Luton, who believed that this route would be less painful and irritating for acidic, irritating, or slowly absorbed drugs.

Pasteur, Lister, and Koch all contributed to discovery of the germ theory of disease, concerns for sterility, use of aseptic techniques, and development of sterilization methods during the 1860s. However, their concerns for the need to sterilize and maintain sterility of injections were not accepted or implemented for decades. It was not until 1884 that the autoclave was introduced by Charles Chamberland for sterilization purposes. Gaseous sterilization was first discovered using formaldehyde in 1859 and ethylene oxide in 1944. It was also in the early 1940s that radiation, beginning with ultraviolet light, was used as a means of sterilization.

Filtration methods began in the mid-1850s when Fick described "ultrafilter" membranes on ceramic thimbles by dipping them in a solution of nitrocellulose in ether. Crude filters, using asbestos, began to be used in the 1890s. Zsigmondy and Bachmann in 1918 coined the term "membrane filter." Beckhold developed a method to determine the pore size of membrane filters, the method we know now as the "bubble point" method.

Pyrogenic reactions were still commonplace until Florence Siebert in 1923 discovered the cause of these reactions. She was the first person to suggest that fever reactions after injections were microbial in origin. She also proposed that these microbial derivatives were nonliving, nonproteinaceous, and could not be eliminated by sterilization methods. Also, she developed the rabbit pyrogen test, used for decades for the detection of pyrogenic contamination, and still a USP method, although most products today are tested for bacterial endotoxin by the Limulus Amebocyte Lysate (LAL) test discovered by the Johns Hopkins researchers, Levin and Bang in 1964.

Intravenous nutrition using hyperalimentation solutions started in 1937 when W. C. Rose identified amino acids as necessary for the growth and development of rats. This mode of therapy was established first in dogs and then in humans (1967) by S. J. Dudrick who developed a safe method for long-term catheterization of the subclavian vein that permitted these highly concentrated and hyperosmolar solutions to be administered without damaging venous vessels.

Although the first book to be used as a standard for national use, the United States Pharmacopeia, was published in 1820, it was not until the fifth edition of the National Formulary in 1926 that the first parenteral monographs were accepted. In 1938, the Food, Drug, Cosmetic (FD&C) Act was passed by Congress after the sulfanilamide disaster where 107 people including many children died after ingesting a liquid form of this drug dissolved in diethylene glycol. This Act also established the Food and Drug Administration to enforce the Act and required manufacturers to prove to the government that drug products introduced into the marketplace were safe. The legal basis for cGMPs and other FDA regulations are related to the 1938 FD&C Act.

Penicillin started being used in the 1940s, further opening the door for parenteral therapy as a means to save thousands of lives. More companies started to develop parenteral drugs. Because so many injectable drugs were unstable in solution and because of the need to provide blood in a stable form during World War II, freeze-drying was introduced in 1942.