

1976–2001

25 Years of Change in the Parenteral Technology Field

Michael J. Akers

The author reflects on the state of the parenteral drug industry in 1976; remarkable advances made in the general pharmaceutical industry, clinical practice, and education during the past 25 years; and what's in store for the next quarter century.

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In 1976 I was a senior scientist in the pharmaceutical development department of Alcon Laboratories in Fort Worth, Texas. At that time Alcon employed about 250 technical people. How much that company has grown in the past 25 years! One year later I moved to Memphis to teach and do research at the University of Tennessee College of Pharmacy. I helped Dr. Kenneth Avis teach summer postgraduate parenteral medications courses, which back then were two weeks in duration (including Saturdays!). Today those courses still exist, although now they are only one week long.

As I look back over the past 25 years in the field to which I chose to devote my career, I note that, as in any other highly technical field, significant changes and advances have occurred. Many readers may not be aware that 25 years ago, from a general pharmaceutical industry, clinical practice, and education standpoint,

- CGMPs (Part 211) were still in the proposal stage and didn't become official for another two years.
- Very few schools of pharmacy offered a PharmD degree.
- FDA inspections were general biannual visits with weak enforcement of compliance to as-then unofficial GMP regulations.

“You cannot do today's job with yesterday's methods and be in business tomorrow.”

Nelson Jackson

- Preapproval inspections and development history reports were unheard of.
- Biotechnology was still in its infancy, with only academic research being pursued. There were no Genentechs, Amgens, Biogens, and all the other “gen” companies as we know them today.
- No one had a desktop or laptop computer.
- Process validation had not been proposed.
- Project management was unheard of.

Then, looking at the field of parenteral science and technology, in 1976:

- Many sterile products were prepared in unclassified environments.
- There was no such thing as “media fills” simulated aseptic processing. In fact, production leaders were horrified at the thought of bringing culture media into a manufacturing environment.
- Technologies such as high-speed filling, barrier isolators, pre-filled syringes, and automated particle counting either were not in existence or were in very early stages of development.
- Injectable microspheres and other depot-delivery systems were still in the basic research stage.
- Ethylene oxide sterilization of devices was state of the art, not radiation sterilization.
- Glass-sealed ampuls were a popular primary container for sterile solutions.

I took time to review the *Bulletin of the Parenteral Drug Association* articles published in 1976. Some of the topics published included:

- introduction of the HIAC particle counter for detection of particulates
- introduction of the *Limulus* amebocyte lysate test for the detection of endotoxin
- use of reverse osmosis to prepare water for injection
- introduction of the proposed CGMP regulations
- introduction of the proposed CGMP regulations for large-volume parenterals
- design concepts for sterile production facilities.

As the old saying declares, “We’ve come a long way, baby!” Today,

- FDA has tremendous power with respect to plant inspections and issuance of warning letters and, when necessary, more serious legal actions.
- Facilities built in the 1970s and even in the 1980s for manufacturing sterile drug products now are outdated. Cleanrooms now are smaller and more highly controlled with respect to air handling and construction materials. Barrier-isolator technologies are now commonplace. Many unit processes such as check weighing, environmental monitoring, freeze-dryer loading, and in-process inspection now are, or soon will be, automated.
- Approximately 40 proteins have been prepared from recombinant-DNA technology in commercial products. More than 300 potential new products from biotechnology are in clinical development and will be used to treat more than 200 disease states.
- Requirements for validation of all processes and methods have exploded. Think of what has occurred even in recent years with respect to cleaning validation, computer system validation, aseptic processing validation, and general requirements for total process and methods validation in new drug application submissions.
- The science of freeze-drying has advanced greatly, and the majority of biotechnology medicines requires this type of processing.
- Several long-acting (weeks to months) depot injections now are commercialized.

“Two basic rules of life:

(1) Change is inevitable.

(2) Everyone resists change.

Remember this: When you are through changing ... you’re through.”

Source unknown

- Outsourcing and contract manufacturing have exploded, possibly as the result of so many company mergers and budget constraints related to facility expansions and new plants.

Where will the next 25 years take us in this field of parenteral technology? Everyone is entitled to his or her opinions, and here are mine:

- Dispersed system formulations (microspheres, liposomes, and other microparticulate delivery systems) for delivery of DNA-based drugs (“genome pharmaceuticals”) will be prominent as commercial products in the same way that solutions and freeze-dried products are today.
- “Seamless” processing will be standard practice in which the production of the active pharmaceutical ingredient (API) and the production of finished dosage forms will be continuous. APIs in the form of genes likely will be cryopreserved and never isolated as dry solids.
- Human operators no longer will be directly involved in sterile processing. Automation and isolator technologies will be in vogue.
- Advances in syringe technologies will make this packaging delivery system more prominent than the rubber-closed vial.
- Sterilization technologies (radiation, light, new gaseous agents, and so forth) will advance to the point at which terminal sterilization procedures can be applied to a larger proportion of finished dosage forms.
- Filtration systems will be developed and must be validated for removal of viruses in the filtration of genomic pharmaceuticals.

What an intriguing, exciting world of science and technology we live in. Let’s witness, learn, and contribute together and expect even more and greater changes during the next 25 years than have occurred during the past 25 years. **PT**