The advent of syringes dates back more than 100 years, when in the 1850s Alexander Wood, a Scottish physician, and Charles Gabriel Pravaz, a French surgeon, independently developed the signature drug administration implement with the hollow, pointed needle. Despite generally being considered a medical device, when prefilled, the syringe also serves as a method of primary packaging.

Today, prefilled syringes provide product differentiation for a host of drugs and vaccines. They are particularly compatible with emergency and self-administered medications because of their ease of use and immediate availability. Prefilled syringes also are well suited for holding diluent for lyophilized drugs and eliminating the first step in the reconstitution process.

Ben Venue Laboratories (Bedford, OH), a contract manufacturer of sterile pharmaceuticals, designed a checklist to aid customers who are transitioning to the use of prefilled syringes. According to this checklist, prefilled syringes offer numerous safety benefits such as tamper evidence, incompatibility with reuse, highly accurate dosing, and “reduced potential for mixups, because the product can be clearly identified by labeling or printing on its barrel.” Ben Venue’s closed filling system can accommodate glass or plastic syringes that can be supplied with needle shields (Schott Prefillable Syringe System, Schott Pharmaceutical Packaging, Inc., Cleona, PA). The syringe is produced from borosilicate glass to high tolerance standards in diameter and thickness (Schott forma 3s). Inert cycloolefin polymer imparts a glass-like transparency and a high chemical resistance to the plastic syringe (Schott TopPac).

Prefilled syringe designs vary but tend to be offered in both assembled needle and Luer Lock configurations. Volumes generally range from 0.5–10 mL. Because each syringe holds a unit dose, the labor and error potential inherent in dose calculation and measurement are reduced. Less time spent handling the medication also means less chance of exposure to particulates or other contamination as well as improved productivity for the administrator.

One caveat, according to the Ben Venue checklist, is that “prefillable syringes are only appropriate when a dosage is to be uniform across the entire patient base.” Compatibility issues can arise, particularly with designs that have product contact parts made of steel, plastic, or silicone-coated glass. Latex parts also may pose a problem if used as part of the design. Finally, prefillable syringes may require more storage space and carry a higher price compared with single- and multiuse vials.

Ben Venue’s checklist advises adopting the prefillable syringe early in the drug development process, ideally during Phase II clinical trials so that no additional compatibility studies are required. Delaying the adoption of a prefillable syringe until much later in the process will necessitate filing a packaging supplement. For products already on the market, converting to prefilled syringes will require new stability studies.

Needlesticks
No doubt the first accidental needlestick occurred not long after the syringe was invented. In the interim, population growth, an ever-expanding use of syringes and other sharp objects or “sharps,” and the emergence of deadly bloodborne viruses have combined to make needlestick incidents far too frequent and a significant hazard for healthcare workers. In March 2000, the Centers for Disease Control (CDC, Atlanta, GA) estimated that 600,000–800,000 injuries per year result from contaminated sharps. According to data from CDC and the Exposure Prevention Information Network (EPINET) database coordinated by the University of Virginia (Charlottesville, VA), syringes are the most common culprit of sharps injuries. Worse still,
Prevention of Sharps Injuries (NAPPSI, Carlsbad, CA) divides needlestick safety products into two groups: primary prevention and secondary prevention. Primary prevention eliminates the needle or other medical sharp, and secondary prevention adds a level of protection to any sharps in the workplace. “NAPPSI is focused on primary prevention,” says executive director Brad Poulos. “But sometimes you can’t eliminate the needle because the technology doesn’t exist; it’s still developing.” For example, today needleless injectors are not suitable for some vaccines or deeply injected drugs.

The operational key to needleless injectors is to send the liquid or powder through a tiny orifice with enough force to penetrate tissue subcutaneously or, in some cases, intramuscularly. Most designs rely on interchangeable vials and a repository for the medication (Biojector 2000, Bioject, Inc., Rockland, MA; Syrjet Needleless Injector, Keystone Industries, Cherry Hill, NJ), but single-use designs are available and used. Manufacturers of needleless drug delivery systems are developing standards under the auspices of the Association of Needle-Free Injection Manufacturers (East Syracuse, NY).

A prefilled, single-use needleless injector has been commercialized both by Pharmacia Corp. (Peapack, NJ) for Fragmin anticoagulation therapy and by GlaxoSmithKline (Research Triangle Park, NC) for Imigran/Imitrex migraine treatment. The device is constructed of a borosilicate glass ampul prefilled with ≈1 mL of product, an actuator or power source, and the trigger mechanism. During use, the patient or caregiver removes the snap-off tip, tears the safety band, and presses the device lightly but firmly against the skin. The contact triggers the actuator and propels the drug subcutaneously or intradermally. Dispensing typically requires less than 5 s. An ordinary trash receptacle can be used for disposal of the needle-free injector (Intraject, Weston Medical Group Plc, Cambridge, England).

A somewhat different needleless injector is designed for dispensing powders rather than liquids (Dermal Powderject ND-Disposable, Powderject Technologies, Fremont, CA). The unit relies on helium gas to propel a premeasured dose of dry solid powder at a velocity sufficient to breach the skin. This delivery method is compatible with traditional small molecules, peptides, proteins, vaccines, or DNA. In operation, when

**OSHA Bloodborne Pathogens Standard**

To meet requirements of the Needlestick Safety and Prevention Act, OSHA revised its 1991 Bloodborne Pathogens Standard. Published in the Federal Register on 18 January 2001, the new regulations (21 CFR 1910.1030) took effect on 18 April 2001, although enforcement did not begin until 17 July 2001. New provisions require employers to maintain a sharps injury log, involve nonmanagerial employees in an annual review and selection of safer needle devices, and update the organization’s written exposure control plan documenting the evaluation process and implementation of any new engineering controls. The revised standard also clarifies what the original meant by “engineering controls” by defining the term as “e.g., sharps disposal containers, self-sheathing needles, safer medical devices such as sharps with engineered sharps injury protections, and needleless systems.” The standard applies to any employer whose workers are exposed to blood or other potentially infectious materials. Workplaces with 10 or fewer employees are exempt from OSHA recordkeeping mandates and aren’t required to establish a sharps injury log.

several hundred of these injured healthcare workers subsequently will become infected with HIV or hepatitis B or C.

With the congressional passage in late 2000 of the Needlestick Safety and Prevention Act and subsequent revision of the Bloodborne Pathogens Standard by the Occupational Safety & Health Administration (OSHA, Washington, DC), needlestick prevention is garnering even greater attention.

Although it’s too early to determine whether the revised Bloodborne Pathogens Standard and various state laws related to needlesticks will reduce the number of injuries, one determinable reduction factor is the growing number of safety syringes available in both conventional and prefilled configurations.

The National Alliance for the Primary Prevention of Sharps Injuries (NAPPSI, Carlsbad, CA) divides needlestick safety products into two groups: primary prevention and secondary prevention. Primary prevention eliminates the needle or other medical sharp, and secondary prevention adds a level of protection to any sharps in the workplace. “NAPPSI is focused on primary prevention,” says executive director Brad Poulos. “But sometimes you can’t eliminate the needle because the technology doesn’t exist; it’s still developing.” For example, today needleless injectors are not suitable for some vaccines or deeply injected drugs.

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placed in position on the skin, an actuation pin breaks the tip of the helium-filled microcylinder. The force of the escaping compressed gas opens the drug cassette and delivers the drug.

Other suppliers are focusing on secondary protection and adding active or passive needle-shielding features to both standard and prefilled syringes. Passive devices are considered by many to be superior because the protective feature works automatically without any intervention by the caregiver. Unfortunately, CDC data show about one-fourth of all needlestick injuries occur in situations in which a safety feature is present but not activated.

One of the first promoters of a prefilled safety syringe for a vaccine is GlaxoSmithKline. Compliant with the Bloodborne Pathogens Standard, the GSK Safety Tip-Lok system (Tip-Lok Syringe/BD SafetyGlide, Becton, Dickinson and Co., Franklin Lakes, NJ) is used for pediatric doses of Havrix (hepatitis A vaccine inactivated) and Engerix-B (hepatitis B vaccine recombinant). When activated, a shield drops over the needle tip.

A retractable needle is the protective feature on a prefilled syringe with either a prefixed needle or a Luer Lock (Prefilled Syringe, Apis Medical BV, The Hague, The Netherlands). The single-use design reportedly is inexpensive to produce, simple to assemble, and compatible with standard injection systems.

Morphine sulfate from Amphastar (Rancho Cucamonga, CA) combines a safety needle with latex-free construction for a range of concentrations (Dilute-A-Jet Prefilled Syringe, International Medication Systems, Ltd., South El Monte, CA).

Various square-bodied, easy-to-grip needle guards that are designed especially for prefilled glass syringes and cartridges snap onto the barrel. Trans-
About one-fourth of all needlestick injuries occur in situations in which a safety feature is not activated.

Parent plastic reveals cartridge and syringe markings, labels, and contents. Different colors designate different syringe sizes; e.g., yellow for 0.5 mL, purple for 1.0 mL, orange for 1.0 mL long, blue for 1.5 mL, and red for 2.25 mL. After the injection is given, the guard slides forward to cover the needle and locks into place (UltraSafe, Safety-Syringes, Inc., Carlsbad, CA).

Like their prefilled syringe counterparts, medication cartridges also rely on safety devices such as a protective sheath. The preplaced sheath is activated through pressure against a flat surface after the cartridge has been inserted and the injection given (Needle-Pro for Carpuject Prefilled Medication Cartridges, Portex, Inc., Keene, NH).

FDA considers rules

FDA may expand its role in the fight to prevent needlestick injuries. On 20 June 2002 the agency published an advance notice of proposed ruling (ANPR) related to needle-bearing devices (Docket No. 01P-0120). On the basis of a petition filed jointly by Public Citizen’s Health Research Group (Washington, DC) and the Service Employees International Union (Washington, DC), FDA is requesting comments about banning i.v. catheters, blood collection devices (needles and tube holders), blood collection needle sets, glass capillary tubes, and needle-containing i.v. infusion equipment that do not meet the criteria identified in FDA’s 16 April 1992 safety alert. The petition also asked FDA to issue performance standards based on the five design criteria identified in its safety alert and requested that conventional syringes be labeled with the statement “to prevent possible exposure to HIV and hepatitis, do not use for standard blood draws.”

FDA already has received many responses to the advance notice. Commenting in favor of the ban, James Reed of Medamicus Inc. (Minneapolis, MN)
Many healthcare providers, particularly physicians, indicate that they will only use safety products if and when they are forced to do so. Until a complete ban on nonsafe devices is implemented, the financial and human costs of sharps injuries will continue to mount.

A comment against the ban from Victor Kovner, PhD, of the Travelers Immunization Center (Studio City, CA) attributes needlestick injuries to “poor training, poor habits, and the hurried environment caused by a failed US healthcare system. New devices and new regulations will only add to the burden and cost without solving the problem.”

Beth Slingluff of Carondelet Health Network (Tucson, AZ) believes a ban would cause shortages because manufacturers of needleless and safety devices are already struggling to keep up with demand. She also notes that new device designs sometimes are incompatible with existing systems, rendering such a ban impractical.

The deadline for comments about FDA’s ANPR is 19 September 2002. Electronic submissions may be made at http://www.fda.gov/dockets/ecomments.

Meanwhile, the ECRI (formerly the Emergency Care Research Institute, Plymouth Meeting, PA) recommends “go needleless whenever you can.” To help healthcare facilities learn what options are available, the group tests and evaluates products and publishes a selection guide. The 2001 Sharps Safety and Needlestick Prevention report is available for $195 for members of ECRI’s Health Devices System, Select-Plus, and Healthcare Risk Control System and $295 for nonmembers.

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**Correction**

In the article “Novel Approaches for Topical Delivery of Acetazolamide,” in our July 2002 issue, the structure of acetazolamide in Figure 1 mistakenly was published without sulfur as a component. The correct figure is as follows:

![Correction Figure]

Acetazolamide is $N$-(5-sulphamoyl-1,3,4-thiadiazol-2-yl)-acetamide

We apologize for this error and any inconvenience or misunderstanding it may have caused.