
Status Report on the Uniject™ Prefilled Injection Device

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History of the Uniject Device

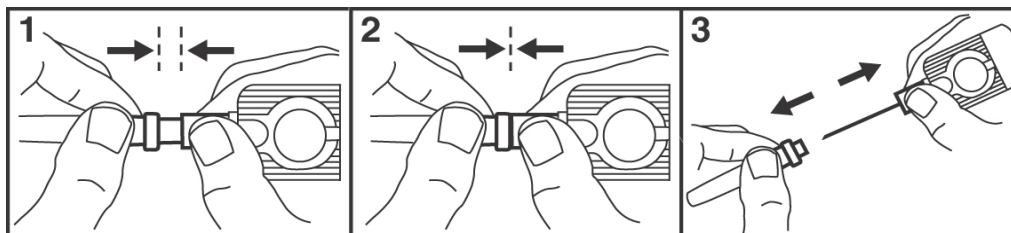
A decade ago, prefilled syringes were too costly for use in public-sector health programs, and no prefilled syringe on the market offered an auto-disable feature. With support primarily from the United States Agency for International Development (USAID), under the Technologies for Health (HealthTech) project, and guidance from the World Health Organization (WHO) and a multitude of other collaborators, PATH developed an auto-disable, prefilled syringe known as the Uniject™* device. Today, the Uniject device is licensed to Becton Dickinson (BD), the world's largest manufacturer of injection equipment, for commercial production and distribution. This report provides an update to public-sector agencies on the status of the Uniject device.



The Uniject Device

Description of the Uniject Device

The Uniject device is a prefilled, single-dose injection device specifically designed to prevent attempts at reuse. It combines drug or biological, syringe, and needle packaged in a sealed foil pouch. Uniject devices are available in 0.25-, 0.5-, and 1.0-ml dose sizes and can be ordered with any standard needle size.



Instructions for Using the Uniject Device

* Uniject is a trademark of BD.

Rationale for the Uniject Device

The Uniject device was designed with the following features in mind:

- **Single dose**—to minimize wastage and facilitate outreach to individual patients.
- **Prefilled**—to ensure that the correct dose is given, and to simplify procurement and distribution logistics.
- **Nonreusable**—to minimize patient-to-patient transmission of bloodborne pathogens.
- **Easy-to-use**—to allow self-injection and use by health workers who do not normally give injections, and to facilitate use in emergency situations.
- **Compact size**—for easy transport and disposal.



**Uniject Production at
BD Singapore**

Production Status

BD produces Uniject devices in Singapore with a fully automated, high-volume production line and markets them globally to pharmaceutical companies through their regional sales offices.

The process required for a pharmaceutical company to offer a drug or biological in the Uniject device is more complex than one might expect, and usually includes the following steps:

1. Identification of the potential market for the product.
2. Pilot fills into Uniject devices using equipment loaned by BD.
3. Compatibility and stability testing of the Uniject/drug combination.
4. Clinical or user-acceptability studies (if required).
5. Purchase, installation, and validation of processing equipment.
6. Completion of regulatory approval processes for the Uniject/drug combination.

From start to finish, the process listed above can be expected to take a minimum of two to three years. Fortunately, over 30 pharmaceutical company projects have entered into the process. The targeted drugs include vaccines, injectable contraceptives, uterotonics, and analgesics. Approximately 20 companies have already conducted pilot fills, and 9 have committed to the installation of equipment for filling and packing of Uniject. The first commercial product in the Uniject device became available in 2000. Today the following products are available in the Uniject device: hepatitis B vaccine and tetanus toxoid (TT) from P.T. BioFarma (Indonesia) and hepatitis B vaccine from Lab Pablo Cassara (Argentina).



**Uniject Packaging Line
at PT BioFarma**

Summary of Clinical and Field Experience With the Uniject Device

Table 1: Summary of Uniject Device Studies and Introduction Activities

Date	Drug or Biological	Country	Site	Focus
1991-1992	Prostaglandin	Egypt ¹	Hospital	Acceptability
1991	Prostaglandin	India ²	Hospital	Acceptability
1995	Tetanus toxoid	Bolivia ³	Homes	Acceptability, use by traditional birth attendants
1995-1996	Tetanus toxoid and hepatitis B vaccine	Indonesia ^{4,5}	Homes	Acceptability, immunogenicity of hepatitis B vaccine
1995-1996	Cyclofem	Brazil ⁶	Clinic	Acceptability
1997	Cyclofem	Brazil ⁷	Clinic	Self-administration
1998-2000	Oxytocin	Angola	Hospital	Acceptability, clinical effectiveness
1999-2000	Oxytocin	Indonesia	Homes	Acceptability, use by village midwives
1999-2000	Cyclofem	Mexico	Clinic/Homes	Introduction, self-administration
1999-2000	Hepatitis A vaccine	United States	Outpatient clinic	Provider acceptability, clinical equivalence with syringe
2000-2003	Hepatitis B vaccine	Indonesia	Clinic/Homes	Nationwide introduction of home-delivery birth dose
2003-2004	Hepatitis B vaccine	Vietnam (planned)	Homes	Introduction
2003	Hepatitis B vaccine	China	Homes/Hospital	Demonstration project
2003	Tetanus toxoid	Afghanistan, Burkina Faso, Ghana, Mali, Somalia, Southern Sudan	Outreach campaign	Introduction

The above studies occurred with the collaboration of pharmaceutical companies that conducted pilot fills of drugs or biologicals into Uniject devices and met regulatory requirements to release the products for clinical use. Early studies focused on the acceptability of using the Uniject device to deliver drugs in difficult situations, e.g., administration of uterotonic drugs such as oxytocin to prevent or treat postpartum hemorrhage,^{1,2} or administration of vaccine to women and children in their homes.^{3,4,5} In the case of hepatitis B vaccine, the vaccine must be given as close to birth as possible in locations where perinatal transmission is high—meaning that home administration is essential when births take place in the home. A few studies focused on use of the Uniject device by individuals who do not normally give injections.^{3,7} Results of studies thus far have revealed the following:

- The Uniject device was found to be easier to use than a standard needle and syringe and was preferred over a standard needle and syringe.^{2,3,4,6}
- Uniject devices facilitate outreach programs and, in certain circumstances, are able to be stored outside of the cold chain.^{3,4}
- Individuals who had never delivered an injection were able to successfully do so with the Uniject device after minimal training.^{3,7}

- No significant differences were found in seroconversion rates or geometric mean titers of hepatitis B surface antibody between three groups of infants receiving hepatitis B vaccine stored: (1) in the cold chain and delivered with standard needles and syringes, (2) in the cold chain in the Uniject device, and (3) at ambient temperatures in the Uniject device for up to one month.⁵
- With specific training, aspiration is achievable with the Uniject device.⁶
- As with any syringe/needle combination, users must be trained not to recap Uniject devices after use.^{3,4}
- Some aspects of using the Uniject device were found to be difficult by some users of early prototype devices (e.g., the activation step,^{2,4,6} pressure required to collapse the blister,⁶ and removal of the needle shield³). BD has since improved the device to make these steps easier.
- Self-administration of injectable contraceptives using the Uniject device is possible.⁷

Oxytocin and the Uniject Device

Two studies were designed to use the Uniject device to administer oxytocin to women for routine management of the third stage of labor to reduce the incidence of postpartum hemorrhage. Both studies assessed the acceptability of this method to women and health care providers, as well as training and logistical issues. Karolinska Institute, in collaboration with the WHO Safe Motherhood Programme, conducted a study in Angola in which midwives in two maternity units (one central and one peripheral) used 1,500 oxytocin-filled Uniject devices. PATH, in collaboration with WHO/Indonesia and the Indonesian Ministry of Health, conducted a second study in Indonesia. In this study, village-based midwives successfully used 2,200 oxytocin-filled Uniject devices during home deliveries. The results of the Indonesia study will be published in late 2003. Additional studies are being planned to assess the feasibility and acceptability of using oxytocin-Uniject in facility-based and community-based settings by both skilled and health workers and specially trained community members. An Indian pharmaceutical manufacturer is filling oxytocin in the Uniject device for use in these field trials.

Gentamicin and the Uniject Device

WHO estimates that at least four million neonatal deaths occur around the world every year, the majority of them caused by severe bacterial infections. Ampicillin and gentamicin are the standard therapy for these bacterial infections, and therapy is based on the weight of the neonate. In order to provide gentamicin in a prefilled format in the Uniject device, a study was conducted in 2003 to verify appropriate dosages based on weight categories of neonates. Currently, the process of filling gentamicin in the Uniject device is underway with an Indian pharmaceutical manufacturer. The product from this fill will be used in an upcoming study in collaboration with the Saving Newborn Lives Initiative with Save the Children Federation in Bangladesh. The study will assess the feasibility and acceptability of the use of the gentamicin-Uniject device to treat neonatal sepsis in the home by community health workers and in health care facilities by nurses.

Vaccines and the Uniject Device

Hepatitis B vaccine and TT in the Uniject device are on the verge of wide-scale availability. Introductions are taking place in several countries, with special attention being paid to:

- *Logistics*—cold chain, storage, and transport
- *Increasing coverage*—targeting hard to reach or underserved areas
- *Disposal*—safe sharps disposal
- *Cost evaluation*—costs of introducing the Uniject device in developing-country immunization programs

Hepatitis B Vaccine

As of 2003, with assistance from Global Alliance for Vaccines and Immunization (GAVI) and The Vaccine Fund, Indonesia is providing the birth dose of hepatitis B vaccine in the Uniject device to all infants born in Indonesia. The Indonesian producer, Bio Farma, is working towards WHO prequalification of hepatitis B vaccine in the Uniject device. Once achieved, this product will be available to countries receiving vaccines from GAVI. Vietnam plans a rapid, wide-scale introduction of birth-dose delivery of hepatitis B vaccine in the Uniject device as soon as WHO prequalification of the product is complete.



Infant Receiving Hepatitis B Vaccine in the Uniject Device (Indonesia)

Following are other sources of hepatitis B vaccine in the Uniject device:

- Hepatitis B in the Uniject device is commercially available in Argentina from Lab Pablo Cassara. However, this is primarily for private-sector distribution, as the company is not a WHO prequalified supplier.
- Beijing-Tiantan Biologics Institute has Chinese regulatory approval for hepatitis B vaccine in the Uniject device and will have 120,000 units available for a demonstration project and test marketing by mid-2003.
- Three hepatitis B vaccine producers in India are in the process of installing Uniject device filling and processing equipment. One of the firms expects to launch its hepatitis B-Uniject in mid 2003.

Tetanus Toxoid

The United Nations Children's Fund (UNICEF) has identified the Uniject device as an important tool in their efforts to eliminate maternal and neonatal tetanus in high-risk areas around the world. The global introduction of nine million doses of TT in the Uniject device was made possible by the five-year (1998-2003) tetanus elimination initiative launched by UNICEF and BD entitled "Partnership for Child Health." BD donated both a Uniject processing line and the Uniject devices. Bio Farma and LifeLines Technology, Inc., donated the TT and vaccine vial monitors (VVMs), respectively. BioFarma achieved WHO prequalification of the product in mid-2001.

Operational research to assess the potential of incorporating TT in the Uniject device into immunization programs were conducted in Afghanistan, Mali and Ghana in 2003. Factors that were looked at include safety, coverage, logistics, and cost. In 2003, several other countries are also targeted for introductions of TT in the Uniject device, including Burkina Faso, Somalia, and Southern Sudan. The Uniject device is expected to be especially effective in reaching women who have not previously been immunized due to ethnic or religious differences or limited health infrastructure.

Cost-Effectiveness

Hepatitis B-Uniject was introduced in three provinces in Indonesia in 2001, and the following year a retrospective study was done to look at the incremental costs or cost savings associated with its introduction. The study found that hepatitis B in the Uniject device was cost saving. Although the gross cost per injection was less for vaccine and disposable syringe compared to Uniject, adjusting for wastage substantially reduced any price advantages. Even at a conservative estimate of 20 percent vaccine wastage, the incremental cost of US\$0.06 per fully immunized child was marginal, especially considering the potential health benefit of increasing birth-dose coverage, improving injection safety, and reducing hepatitis B transmission rates. In addition, using midwives to administer the birth dose injection was cost saving, despite additional costs associated with midwives' home visits.

With support from PATH, Mexico's Institute of Public Health developed a cost-effectiveness model to evaluate the potential use of the Uniject device in Mexico's national immunization activities. The model is flexible enough to assess different vaccine and delivery system combinations in any country setting. Another cost analysis is currently being finalized for the 2003 TT campaign in Ghana. This evaluation is looking at the costs of introducing the Uniject device in large immunization campaigns in rural, high-risk areas for all women of fertile age. A study will also be conducted in China to evaluate the incremental costs of delivering the birth dose of hepatitis B in the Uniject device outside the cold chain.

Injectable Contraceptives and the Uniject Device

***Cyclofem*™†**

From September 1999 to February 2000, three major family planning service providers in Mexico conducted a comparative survey to evaluate the acceptability of Cyclofem in the Uniject device with 750 women and their health care providers. One-half of the participating women successfully administered five monthly injections to themselves at home after giving themselves an injection in the clinic under supervision.

Two studies, published in 1996 and 1997, were conducted in Brazil with Cyclofem in Uniject devices.^{6,7} The first assessed the acceptability of the product for both health care providers (who administered the injection) and patients. Ninety percent of the service providers reported that Uniject was easy to activate and inject and that it was reassuring for users to know that the syringe and needle had never been used previously. The second study evaluated women's acceptance of and ability to self-administer the contraceptive using Uniject devices. More than

† Cyclofem is a registered trademark of The Concept Foundation.

90% of self-administered injections were successful and 57% of women who self-injected preferred this method of injection and said that they wished to continue with the self-administration.

Depot-Mexdrogesterone Acetate (DMPA)

A multinational pharmaceutical company conducted stability/compatibility trials of a reformulated DMPA in Uniject.

Uniject Introduction Issues

A few topics deserve special attention when introducing the Uniject device into health programs. These include cost-effectiveness, storage capacity, training, and disposal.

Cost-Effectiveness

A variety of cost factors need to be taken into account when analyzing the appropriateness of the Uniject device as an injection system for a specific application, including:

- *Cost per dose*—A prefilled Uniject device replaces a vial, syringe, and needle.
- *Wastage reduction*—Savings are likely to be realized when shifting from multi-dose vials to a single-dose format.
- *Logistics and labor*—The prefilled format simplifies ordering, ensures that a sterile syringe and needle are available with each dose of drug, and minimizes labor costs, e.g., preparation of drugs for injection and syringe sterilization.
- *Safety*—As with other auto-disable syringes, decreasing the likelihood of patient-to-patient transmission of bloodborne pathogens via syringe and needle reuse or improper sterilization results in long-term savings to health programs.
- *Disposal*—If disposable or auto-disable syringes are currently in use, disposal costs are likely to decrease with use of the Uniject device, since in both weight and volume, Uniject devices are one third that of AD syringes. If sterilizable syringes are in use, disposal costs are likely to increase.
- *Expansion of services*—While difficult to quantify, the Uniject device can be used in novel ways to increase access to medications. For example, the Uniject device can facilitate immunization outreach, use beyond the cold chain (especially when VVMs are used), home use, self-injection, and use by health workers who do not normally administer injections.

Cold Chain Storage Capacity

The single-dose format of the Uniject device will require more cold chain volume than multi-dose vials. For that reason, if drugs must be refrigerated, volume estimates must be made to see if current cold chain storage capacity is adequate to accommodate a move to a single-dose format. Uniject vaccines are presently packaged 125 per box and occupy 3 liters or 24 cm³ per dose. In the future, multivalent vaccines in the Uniject device may offset the increased storage requirements for the single-dose format. Increased distribution schedules can also decrease storage capacity requirements.

Many drugs and vaccines, like tetanus and hepatitis B, are heat stable and can be transported, stored, and used with less cold chain protection than the less-stable vaccines such as oral polio or

measles. These heat-stable products can spend longer out of the cold chain without being damaged by heat, and therefore use less cold chain storage space. To ensure that vaccines have not been damaged by heat, a Vaccine Vial Monitor (VVM) should be attached to the outside of each package of Uniject. VVMs change color to show when the vaccine has been exposed to too much heat and should not be used.

Training

Experience has shown that training health personnel to use Uniject is a brief and simple process. Health worker training can be accomplished within one to two hours. The training includes instruction on proper use and disposal of Uniject, review of safe injection procedures, VVMs, and practice with the device.

Certain issues require reinforcement during training. These include:

- Activation step to open flow from drug reservoir.
- Hand placement to avoid accidental expulsion of the drug.
- Proper injection at a downward angle.
- Prevention of recapping.

Disposal

If not already in place, it is important to plan for an effective disposal system before Uniject devices are introduced. One benefit of the Uniject device is that it contains only about 35 percent of the amount of plastic of a standard disposable syringe. It weighs significantly less than a disposable syringe and single-dose vial. The plastics used in Uniject devices can be incinerated without the generation of toxic fumes, such as those produced by the rubber piston in standard disposable syringes. When incinerated, the basic polymer ingredients of carbon, hydrogen, and oxygen convert to water and carbon dioxide. These materials can usually be safely discharged into the atmosphere.



Uniject Outreach Carrier

In instances where Uniject devices are used for outreach, it is recommended that health workers transport and store devices in a protective outreach carrier. In studies on the Uniject device, PATH has used a small plastic box for this purpose. The outreach carrier contains a compartment that holds 30 Uniject devices in foil pouches and a compartment that holds a removable cardboard disposal box. At regular intervals, the cardboard disposal box is removed, incinerated, and replaced with a new box. At the same time, the health worker can receive a new supply of filled Uniject devices. Programs may develop similar containers and procure them locally.

The Future of the Uniject Device

The full potential of the Uniject device in public health programs has yet to be realized. Some of the most exciting and presumably cost-effective applications such as use with new, expensive, and/or multivalent vaccines remain to be tested. GAVI has resolved to promote the use of vaccine combinations and single-dose delivery devices that facilitate outreach. Such interest may accelerate the availability of new vaccines in the Uniject device via the creation of a powerful public-sector market force. USAID is also supporting efforts to make the injectable contraceptive DMPA available in the Uniject device and to investigate the use of the device to deliver gentamicin for treatment of neonatal sepsis. The combination of these efforts and the commercial efforts of BD should ensure broad-scale availability of a variety of important drugs and vaccines in the Uniject device to the public sector.

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