

A HealthTech Historical Profile

The Uniject Device

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HealthTech Historical Profile: The Uniject Device

The Problem

The World Health Organization (WHO) has estimated that in some countries the percentage of injections given with syringes or needles reused without sterilization is as high as 75 percent.¹ Disposable syringes are frequently reused, and reusable syringes are often improperly sterilized. The risks of transmission of bloodborne pathogens such as hepatitis B and human immunodeficiency virus are great. New methods are required to ensure that a sterile syringe is available for each injectable dose delivered.

Vaccine wastage has also been identified as a major problem for immunization programs especially in developing countries. Wastage of up to 80 percent of vaccines has been recorded in some countries. As new, high-value, combination vaccines become available, wastage will have to be significantly reduced in order to retain the financial viability of immunization programs.

Access to immunization services remains a major issue in countries with growing populations and poor infrastructure. Outreach services are necessary but often involve village health workers with little training, arduous travel over unimproved terrain, and primitive conditions of service delivery. Syringes, needles, and multi-dose vials are difficult to manage and are often unsafe under these conditions. New vaccine administration methods are needed that will address these outreach problems.

Injection safety and access to service remain major impediments to expansion of other programs using injection—including family planning, neonatal services, and obstetrics. New technologies that deliver medications more easily and accurately in hard-to-reach settings will create significant public health benefits.

Technology Solutions/Strategies

Initial discovery and development

In 1987, just as the HealthTech program was being established at PATH, WHO called an important global meeting to discuss these important issues. PATH staff were actively involved in both organizing and participating in the Evaluation Panel for Injection Technologies (EPITECH) which identified the critical looming need for nonreusable (later called auto-disable) syringes. To meet these needs, solutions would have to be cost-effective and practical in a variety of developing-country immunization scenarios. PATH rose to the challenge by presenting several of the first technology designs which were discussed and evaluated at the meeting.

One of the concepts, for a prefilled, single-dose syringe and needle package, had emerged from earlier collaborations with several private-sector partners. During the first phase of work, PATH took its inspiration from an integrated needle/package device prototype that had been developed by Merck but subsequently shelved. PATH collaborated with Merck to learn from their experience; eventually the company turned over its intellectual property to PATH. The Merck prototype—a small, squeezeable tube—was obviously vulnerable to reuse. To address this

problem, in 1987 PATH invented a new design featuring a collapsible blister and Uniject™* was born—an auto-disable, prefill, integrated syringe/package. In July 1987, PATH demonstrated the Uniject device (then called the SafeTject) and other self-destroying injection devices to EPITECH. The panel identified the Uniject device as one of the most promising devices to support immunization programs:



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.

PATH applied for and received two US patents on components of the device in 1989 and 1990. During the development of the device into a prototype that could be demonstrated to potential manufacturers, staff realized that the collapsible blister could be refilled from a pressurized vial in such a way that the Uniject prototype was still susceptible to reuse. This insight led PATH engineers to develop and integrate a one-way valve into Uniject. With this invention, PATH applied for and received another US patent in 1993; the design of the Uniject device reached maturity.

At the same time, PATH conducted a national search for a suitable, qualified private-sector collaborator to further co-develop the technology and to scale it up for manufacturing. Horizon Medical, Inc. (formerly known as Acacia), a small medical device packaging company in California, was selected.

Horizon Medical, Inc., proceeded with pilot production and the development of prototype automated filling systems. Meanwhile, PATH invested in several major laboratory

studies to demonstrate the compatibility and stability of representative vaccines packaged in the plastic. These were essential steps required for the regulatory process.

Validation—summary of clinical and field experience with the Uniject device

PATH recognized that field-use studies, demonstrating successful performance and acceptability of the Uniject device under field conditions, were critical for public health programs to understand and adopt the new technology. Therefore, under HealthTech, PATH designed and led two key studies in 1995 and 1996: in Bolivia with tetanus toxoid in the Uniject device, and in Indonesia with both tetanus toxoid and hepatitis B vaccine in Uniject. In addition to general study design and coordination, PATH staff worked closely with pharmaceutical companies that conducted pilot fills of medicament into the Uniject device and met regulatory requirements to release the products for clinical use. The implementation of the studies and the positive reaction to the published results highlighted public-sector interest in Uniject—contributing directly to BD's 1996 strategic decision to license and commercialize the technology, which is described later.

* Uniject is a trademark of BD.

Table 1 lists the various studies focused on use of the Uniject syringe, both those conducted by PATH and those conducted by third parties. Early studies evaluated the acceptability of using the Uniject device to deliver drugs in novel and/or difficult scenarios, e.g., home administration by relatively untrained health workers of vaccine^{2,3,4} and uterotonic drugs such as oxytocin^{5,6} to prevent or treat postpartum hemorrhage. In the case of hepatitis B vaccine, for example, the vaccine must be given as soon after birth as possible in locations where perinatal transmission is high—meaning that home administration is essential when births take place in the home (as do 80 percent of births in Indonesia). Some studies focused on use of the Uniject device by individuals who do not normally give injections (i.e., traditional birth attendants [TBAs]).^{2, 7, 8, 9, 10,11}

Table 1: Summary of Uniject Device Studies and Introduction Activities

Date	Drug or Biological	Country	Focus (Setting)	Lead Coordinator	PATH Role
1991-1992	Prostaglandin	Egypt	Acceptability (Hospital)	Karolinska Institute and Assiut University	None
1991	Prostaglandin	India ¹²	Acceptability (Hospital)	Unknown	None
1995	Tetanus toxoid	Bolivia ¹³	Acceptability, use by traditional birth attendants (Home); study funded by HT	PATH	Lead*; facilitated supply*
1995-1996	Tetanus toxoid and hepatitis B vaccine	Indonesia ³	Acceptability, immunogenicity of hepatitis B vaccine (Home); study funded by HT	PATH	Lead*; facilitated supply*
1995-1996	Cyclofem	Brazil ¹²	Acceptability (Clinic)	SEMICAMP	Advised; facilitated supply
1997	Cyclofem	Brazil	Self-administration (Clinic)	SEMICAMP	Advised; facilitated supply
1998-2000	Oxytocin	Angola ¹⁴	Acceptability, clinical effectiveness (Hospital)	WHO	Advised; facilitated supply*
1999-2000	Oxytocin	Indonesia ¹⁵	Acceptability, use by village midwives (Home)	PATH	Lead; facilitated supply*
1999-2000	Cyclofem	Mexico	Introduction, self-administration (Clinic/Home)	IMSS	Advised*

Date	Drug or Biological	Country	Focus (Setting)	Lead Coordinator	PATH Role
1999-2000	Hepatitis A vaccine	United States	Provider acceptability, clinical equivalence with syringe (Outpatient clinic)	Johns Hopkins University	None
2000-2003	Hepatitis B vaccine	Indonesia ^{7,8}	Nationwide introduction of home-delivery birth dose (Clinic/Home)	Indonesian MOH and PATH Children's Vaccine Program (CVP)	Lead; facilitated supply*
2003	Hepatitis B vaccine	China	Demonstration project (Hospital/Home)	PATH	Lead; facilitated supply*
2003	Tetanus toxoid	Afghanistan, Burkina Faso, Ghana, Mali, Somalia, Southern Sudan	Introduction (Outreach campaign) ¹³	UNICEF	Advised; facilitated supply*
2005	Oxytocin	Vietnam	Oxytocin delivered by midwives	Vietnam MOH and PATH	Study design; facilitated supply*

*Indicates HealthTech-supported study coordination and support activities.

Technology Transfer or Licenses

PATH partnered with industry from the early stages of Uniject design and development. PATH's 1988 license agreement with Horizon Medical created the necessary R&D partnership to prepare the Uniject device for eventual scale-up: prototyping, pilot production, and engineering of filling systems.

By the mid 1990s, PATH and Horizon Medical had the Uniject technology substantially engineered and field evaluation of the device underway. BD (formally Becton Dickinson, and Company) expressed its interest in Uniject as a way for them to offer vaccine and pharmaceutical manufacturers a new, lower-cost platform to fill and market their products in a single-dose, prefilled presentation. Given BD's position as the world's largest manufacturer of syringes, the company was uniquely positioned to take the Uniject device through the final phase: global commercialization. In 1996, PATH and Horizon Medical jointly licensed the Uniject device to BD.

BD is now working with pharmaceutical companies around the world, encouraging them to manufacture and market vaccines, injectable contraceptives, and other medicines packaged in BD's Uniject device. The company invested at least US\$25 million to establish a dedicated manufacturing facility (for the empty Uniject devices) in Singapore and another US\$10 million to launch the product in the global market.

Evolution—medicaments in Uniject, the Uniject applications

The initial catalyst for the device—the challenges facing immunization programs—remains the chief driver of both pharmaceutical company and public-sector interest in Uniject, generally. Indeed, to date vaccines are the only type of medicament commercially available in Uniject. This is set to change, given the potential value that is added from packaging injectable contraceptives, uterotonic drugs, or neonatal antibiotics in the prefill Uniject device.

Today, four companies manufacture and market hepatitis B vaccine (HB-Uniject): PT Bio Farma, of Indonesia (this company was first to launch, in 2000); Lab Pablo Cassara, of Argentina; Shantha Biotechnics, of India; and Panacea, also of India. Two other firms are preparing to enter the HB-Uniject market: VACSERA, of Egypt; and Beijing-Taintan Biologics Insitute, of China. The other vaccine commercially available in the Uniject device is tetanus toxoid (TT-Uniject), produced by Bio Farma. VACSERA is also preparing to produce this product. Further, with regard to vaccines in the Uniject device, development of DPT-HB in Uniject is ongoing at Bio Farma and at Shantha. Finally, two firms are preparing to commercialize injectable contraceptives in the Uniject device: Pfizer which has confirmed that they have already invested US\$6 million on feasibility work for Depo Provera SC in Uniject; and Aplicaciones Farmaceuticas, of Mexico, for Cyclofem in Uniject.



**Uniject Production at
BD Singapore**

The process required for a vaccine or 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 combination of their product filled in the Uniject device.
2. Pilot filling of their product 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 for ongoing filling and packaging of their product in Uniject devices.
6. Completion of regulatory approval processes for the Uniject/drug combination.

From start to finish, the process listed above can take a minimum of two to three years. To facilitate the process and reduce the company's risk, PATH often provides technical assistance and limited in-kind support during this period of time. It is important to distinguish between PATH's development of the Uniject device, that ended when BD licensed the product, and

PATH's continuing assistance for Uniject applications for specific vaccines and drugs, that is ongoing and not always supported with HealthTech funds.

Policy Environment

Involvement of international agencies

Collaborative relationships between HealthTech and international agencies have been essential to the Uniject story, beginning with the EPITECH panel's call for new technologies. Interactions with public-sector agencies have continued throughout the development of commercialization of the Uniject device and now in facilitating industry's and the public health sector's uptake of Uniject in priority areas. The agencies that PATH works with vary with the different applications of Uniject:

- Vaccines: WHO Expanded Programme on Immunization and UNICEF, USAID's immunization programs, ministries of health, and Global Alliance for Vaccines and Immunization (GAVI).
- Injectable contraceptives: USAID Office of Population and USAID cooperating agencies, WHO Human Reproduction Program, UNFPA, and IPPF.
- Uterotonics: USAID Maternal and Child Health Division, WHO Essential Medicines Group, and WHO Maternal Health.

Changes in policy

Hepatitis B vaccine and tetanus toxoid packaged in Uniject devices by PT Bio Farma have already been prequalified by WHO for distribution by UNICEF after several years of discussion and review. Further uptake of these products in Uniject has been slowed in part by lack of available vaccine in Uniject supply capacity. At a lower level, governments have had occasion to change some policies; for example, the Indonesian MOH established a policy stating that all hepatitis B vaccine in Indonesia's public health programs is to be given with Uniject. This has, of course, had the impact of creating a demand of at least 10 to 15 million doses per year of hepatitis B vaccine in Uniject by a major purchaser. To facilitate this, the Indonesian MOH allowed their cadre of trained village midwives to deliver the first dose of hepatitis B vaccine—the first time that these midwives had been allowed to deliver immunizations.

Introduction Phase—Uniject applications (medicaments in Uniject)

Development and validation of the Uniject *device*, via PATH's conduct of field studies and BD's establishment of production of the technology, is complete. Introduction and scale-up of various Uniject *applications with various vaccines and drugs* is ongoing and is the focus of this and much of the following sections. Introduction of a Uniject application proceeds in the three broad steps listed below. PATH's involvement generally centers on the first and second steps.

1. Clarification of need. The public health sector must first evaluate the potential value of a given Uniject application. *Ideally*, the results of the evaluation—coupled with the long-term outlook for purchasing—are made known to pharmaceutical firm(s) which in turn analyze whether investment in development is commercially justifiable (in reality, this process is a significant hurdle—see below in section 6b). HealthTech has supported this step in several ways, including studies that clarify the value proposition—to the public health sector and by helping to select and engage pharmaceutical firms (e.g., prospective manufacturers).

2. Development by a pharmaceutical company. HealthTech has also supported this step by providing technical assistance and/or limited cost-sharing to support the pharmaceutical company's efforts, often as negotiated with them under step 1.

3. Introduction and scale-up. Utilizing registered, commercially available product(s). PATH has often been involved at this stage also, although not always under HealthTech.

Value proposition for a Uniject application—to the public health sector

Making the case for an appropriate application of Uniject generally relies on either, or both, of the following two factors:

- The public health value of increased access or coverage, particularly in relation to Uniject's excellent suitability for outreach programs.
- The overall cost-effectiveness of the prefill Uniject device versus multi-dose vial and disposable syringes, particularly as a function of medicament value and wastage rates (of course, many other cost factors can play a role, depending on the application scenario).



Credit: UNICEF/HQ020263/Giacomo Pirozzi

Suitability for outreach

The Uniject device can facilitate immunization outreach, use beyond the cold chain (especially when vaccine vial monitors [VVMs] are used), home use, self-injection, and use by health workers who do not normally administer injections. This versatility owes to Uniject's unique feature set:

- Single dose—to minimize wastage and facilitate outreach to individual patients.
- Prefilled—to ensure that the correct dose is given and to simplify 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.

Field studies have concluded that Uniject devices facilitate outreach programs,^{2,3} individuals who had never delivered an injection were able to successfully do so with the Uniject device after minimal training,^{2,13} and the Uniject device was preferred over a standard needle and syringe.^{2,3,6,12} Additionally, researchers have concluded that self-administration of injectable contraceptives using the Uniject device is possible.⁷

Overall 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:

- Wastage reduction—Savings are likely to be realized when shifting from multi-dose vials to a single-dose format, especially for newer, high-value vaccines.
- Cost per dose—A prefilled Uniject device replaces a vial, syringe, and needle.
- 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 (due to reduced weight and volume).

Particularly important—with respect to mid- or high-value medicaments—is the tendency for *wastage reduction* to offset the higher gross cost per injection of the Uniject presentation, when Uniject devices replace multi-dose vial and disposable syringe. This was demonstrated in a retrospective study done in 2002 by PATH's Children's Vaccine Program to look at the incremental costs or cost savings associated with introduction of HB-Uniject in three provinces in Indonesia during 2001. The study found that delivery of hepatitis B vaccine in the Uniject device was cost saving when multi-dose vial wastage exceeds 31 percent. Even at a conservative estimate of 20 percent multi-dose vaccine wastage, Uniject's incremental cost of US\$0.06 per fully immunized child was insignificant, 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.¹⁶

With support from PATH, Mexico's Institute of Public Health developed a rigorous cost-effectiveness model in 2001 to evaluate the potential use of the Uniject device in Mexico's national immunization activities.

Procurement/distribution issues

With regard to distribution, the single-dose format of the Uniject device requires more cold chain volume than multi-dose vials. In the future, multivalent vaccines in the Uniject device may offset the increased storage requirements for the single-dose format. Increased distribution frequency can also decrease storage capacity requirements. This approach was adopted by the Indonesian government, enabling the country to switch to hepatitis B vaccine in Uniject without increasing its cold chain capacity.

Buyers (i.e., MOH, vaccine manufacturers)

The distribution of vaccines and medicaments in the Uniject device involves two layers of purchasing. Initially vaccine manufacturers must purchase Uniject blanks from BD. The vaccine manufacturers then fill the blanks with their medicaments and sell it as their own finished product. Uniject offers several advantages that manufacturers can use as marketing features:

- Ease of use for outreach and home births (such as Indonesia's hepatitis B vaccine home birth delivery program).
- Reduced wastage compared to multi-dose vials.
- Improved safety over multi-dose vials and other auto-disable syringes.
- New thimerosal-free, single-dose formulations.
- Appropriateness for self-injection.

Mainstreaming, General Acceptance

The full potential of the use 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, in providing vaccines to countries of the world through The Vaccine Fund, 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. Pfizer, which supplies the majority of DMPA purchased by USAID, is advancing plans to put its new subcutaneous DMPA formulation in Uniject and will likely be the first multinational pharmaceutical company to adopt the Uniject platform. USAID is also interested in the use of the device to deliver gentamicin for treatment of neonatal sepsis. The combination of these initiatives and the commercial efforts of BD will help ensure broad-scale availability of a variety of important drugs and vaccines in the Uniject device to the public sector.

Hurdles/Constraints

Perceptions

A critical—and common—misperception is that vaccine in Uniject can be sold at the same per dose cost as vaccine in multi-dose vials. As with any single-dose vaccine product, Uniject's

single-dose format is more expensive than the multi-dose format. However, once the cost benefits of reduced wastage are taken into account, the single-dose format may be cost saving in many applications. Other benefits, such as improved immunization access and prevention of reuse may be more difficult to quantify, but should be considered in an overall cost-benefit comparison between the Uniject device and multi-dose vials. Cost-effectiveness studies, such as the one recently published in the WHO Bulletin on the use of HB-Uniject in Indonesia, will help increase awareness of the whole system cost and benefit implications of using Uniject.

Another misperception is that PATH benefits monetarily from sales of the Uniject since PATH owns key patents on Uniject technology. This is not the case. PATH does not receive any ongoing royalty or other payments under the PATH-BD license agreement for the Uniject device.

The long lead time and significant investment required of a pharmaceutical company to commercialize a vaccine or drug in Uniject devices remain an important challenge to uptake of the technology. To reduce their risk, pharmaceutical companies would prefer to secure multi-year, advance purchase agreements for the drug or vaccine filled in the device before making this investment commitment. This has not happened. An important driver of this problem is the fact that programmatic benefits of adopting Uniject for a vaccine or drug do not directly accrue to the procurement departments of international agencies or governments. Given the higher per dose cost of a vaccine or drug in Uniject devices, combined with a typical mandate to buy the maximum number of doses with a fixed budget, these critical gatekeepers often resist suggestions to purchase vaccines or drugs in Uniject. That the programmatic benefits of a Uniject application accrue instead at the national level is supported anecdotally by the example of Indonesia's nationwide, newborn hepatitis B vaccination program; Indonesia itself sustains the program, relying on HB-Uniject to render the massive task practicable and, when accounting for wastage reduction, cost saving.

Evidence of Impact

Two compelling Uniject device success stories have emerged in the past three years. First, the Ministry of Health of Indonesia, as an early champion and adopter of the device as a vaccine delivery system, relies on HB-Uniject for its new and successful nationwide birth-dose program. Since 2003—for the first time in history—every newborn in Indonesia now receives the first dose of hepatitis B vaccine within a few hours or days of birth thanks to the Uniject device. The Indonesian government sustains much of the effort from its own resources, and—since 80 percent of births in the country occur in homes—has focused on at-birth home immunization utilizing HB-Uniject. The Ministry of Health considers the Uniject device the only practical way of implementing this program.

Secondly, UNICEF with its partners BD, PATH, and the Bill & Melinda Gates Foundation under the Partnership for Child Health for the elimination of tetanus program has adopted Uniject as a method of administration of tetanus toxoid. The Uniject device is being used to deliver nine million doses of tetanus toxoid to women in remote populations throughout the world, including Afghanistan, Ghana, and Mali. This large-scale deployment of Uniject, often utilizing community volunteers such as TBAs, powerfully demonstrated the devices' excellent suitability for outreach scenarios in difficult to reach areas.

During the same period, major trends with positive implications for Uniject have continued to unfold. These range from the development of higher-value vaccines with long-term backing from GAVI to the increasing desire to eliminate the preservative thimerosal from vaccines. Both approaches will necessitate a shift towards single-dose presentations. Other promising developments for Uniject include an increasing likelihood that DMPA in Uniject could be available to major international donors within three to five years and a recent increase in the number of pharmaceutical companies launching Uniject applications.

BD reports a continuing investment of more than US\$1 million annually to promoting and supporting adoption of the Uniject device by pharmaceutical companies. BD has sold over 43 million units of Uniject devices since 2000 to pharmaceutical firms in Argentina, India, Indonesia, and Mexico. PT Bio Farma, in Indonesia, has been the largest customer to date, accounting for 85 percent of worldwide Uniject sales. However, the picture is evolving with Indian firms' recent launch of Uniject products (HB-Uniject). More and more children and women around the world are obviously receiving their lifesaving vaccines via this innovative HealthTech invention.

Third Party Comments about the Uniject device

“The new concept of combination vaccines in BD Uniject would not only increase the immunization substantially in India but will also change the way immunization is done.”
Mr. Masood Alam, Head of Commercial Operations, India Subcontinent, Chiron Vaccines.

“The Uniject device has gone all the way from the drawing board to realization and has helped literally millions of people,” said Craig Stephens, one of judges for the Tech Museum Alejandro Zafferoni Award, given to PATH for the Uniject device in 2003.

“With Uniject anybody can inject the vaccine. An illiterate midwife who’s never been trained in medicine or birthing can do an absolutely perfect job,” Dr. Francois Gasse, senior project manager for immunization at UNICEF.

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