

# **Technologies for vaccine delivery in the 21<sup>st</sup> century: A white paper of WHO, UNICEF, USAID and PATH**

J. Lloyd



Technet Consultation - 6-10 December 1999  
Harare, Zimbabwe  
VACCINES AND BIOLOGICALS



*World Health Organization, Geneva, 1999*

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## *A White Paper of WHO, UNICEF, USAID and PATH*

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## **1 Vision**

The scope of this vision of future change is limited to the technologies of vaccine delivery in developing countries during the next ten, or so, years. The vision of change is driven principally by the need to transform today's delivery system to be more equitable, safer and more efficient. The 21<sup>st</sup> century brings us reformed health systems that better integrate preventive and curative services, new multi-valent vaccines and technologies for safer administration and simpler distribution.

**We can now envision a vaccine delivery system that does not require refrigeration, is closely integrated with the delivery of drugs, utilises safe, pre-filled injection devices containing single doses of thermostable vaccines and processes waste at the point of use without harm to the environment.**

The rationale for investing in these changes in technology lies firstly, in the conviction that they will help to achieve universal coverage with high quality immunization services. Secondly, the probable consequences of introducing new vaccines, while attempting to maintain the current delivery system, might include :

- ◆ Immunization coverage will remain low in hard-to-reach areas

- ◆ Wastage of high-cost vaccine in traditional multi-dose presentation
- ◆ Public demand for new vaccines depressed by fears of injection safety
- ◆ Cost and managerial burden of the cold chain no longer borne in by governments or donor partners

## 2 Strategy

The strategy to transform vaccine delivery systems is aimed at three critical success factors for immunization services in the next century:

- Equity in access to new vaccines
- Safety of vaccine administration
- Simplicity & efficiency of vaccine delivery

These factors can be significantly impacted by the application of new technologies and their associated training and management systems. These new technologies may be applied in three concurrent phases with the following objectives:

- Safer multi-dose vaccine delivery
  - including waste disposal technologies
- Mono-dose, pre-filled injection devices
- Thermo-stable vaccines delivered in the same way as drugs

The most important anticipated impact on immunization systems are shown in Table 1 below:

<b>Table 1 : Impact of technology change on immunization services</b>			
	<b>Safer multi-dose vaccine delivery</b>	<b>Mono-dose, pre-filled injection devices</b>	<b>Thermo-stable vaccines delivered with drugs</b>
<b>Equity of access to new vaccines</b>	Safe injection devices and disposal technology assured for mass immunization	Ease of administration permits community care providers to immunize. A single dose available to a single child – always. Lowest cost per delivered, multi-valent dose of new vaccine.	Vaccines carried to people wherever they live with no refrigeration impediment. Potency of vaccine assured for every child wherever he/she may live
<b>Safety of vaccine administration</b>	No re-use of syringes possible Reduced needle-stick risks Sterilization assured by monitoring – or eliminated	No re-use of injection devices possible Vaccine dose integrity & sterility guaranteed to the point of use No manual manipulation of the vaccine possible	Elimination of the needle and consequent elimination of needle-stick hazard.
<b>Simplicity and efficiency of vaccine delivery</b>	Progressive elimination of complex and risky sterilization procedures. Progressive improvement in waste management systems. Higher cost for improved safety.	Elimination of administrative vaccine wastage – lower costs. Reduced reliance on refrigeration & icemaking at the peripheral level where 75% of distribution costs are concentrated. Less equipment maintenance. Easier stock control.	Reformed health systems able to integrate fully drugs with vaccines Complete elimination of refrigeration in the distribution system – reduced cost and managerial burden Easier stock control

### 3 Technologies

Technologies not only enable change, but they can also catalyse change by focussing changes of behaviour on visible, tangible difference. The rationale, status and prospects for five key, new technologies are discussed here:

- Auto-disable syringes and safety boxes
- Mono-dose, pre-filled injection devices
- Needle-free injections
- Point-of-use sharps processing
- Thermostable vaccines and Vaccine Vial Monitors

#### 3.1 *Auto-disable syringes & safety boxes*

##### 3.1.1 Rationale

The re-use of standard single-use disposable syringes and needles, which are used to give nearly half of all immunizations, is widespread<sup>1</sup> and the risk of transmission of blood-borne pathogens from patient to patient is high<sup>2</sup>. The resulting disease burden is believed to be higher than that resulting from patient to health worker transmission through accidental needlestick and higher than that resulting from improper disposal. Re-use is the highest risk from unsafe injection practices in developing countries.

The auto-disable (A-D) syringe, which has been assessed in the laboratory and the field<sup>3</sup>, presents the lowest risk of person-to-person transmission of bloodborne pathogen because it is designed to prevent reuse. This syringe is now the disposable equipment of choice for administering vaccines for mass immunization campaigns<sup>4</sup>. Although means for safe disposal are still inadequate in most developing country settings, the risk of non-compliance with sterilization procedures is considered much higher.

“Safety boxes”, puncture proof containers for collecting and disposing of used disposable and auto-disable syringes, needles and other injection materials reduce the risk posed to health staff and the general public by contaminated needles and syringes

##### 3.1.2 Status

A-D syringes are now produced by five manufacturers for supply to immunization services directly, or through UNICEF. It is estimated that over 160 million of these syringes will have been used in 1999, twice the annual demand last year.

Nevertheless, this is only a small fraction of over one billion injections which were given for immunization in developing countries this year.

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<sup>1</sup> “Review: Unsafe injections in the developing world and transmission of blood-borne pathogens Simonsen”, Simonsen L (Ph.D.), Kane A, Lloyd J, Zaffran M, Kane M (M.D.)

<sup>2</sup> “Transmission of Hepatitis B, Hepatitis C and HIV through Unsafe Injections in the Developing World: Model-Based Regional Estimates”, A.Kane et al., awaiting publication WHO Bulletin Autumn 1999.

<sup>3</sup> “Safety, effectiveness and ease of use of a non-re-usable syringe in a developing country immunization programme” R.Steinglass, D. Boyd, MGrabowsly, A.G. Laghari, A. Qavi,& P. Evans: Bulletin of the World Health Organisation, 1995, 73 (1): 57-63

<sup>4</sup> “Safety of Injections: WHO-UNICEF policy statement for mass immunization campaigns”: Issued jointly by the World Health Organisation, Geneva Switzerland, (Global Programme for Vaccines and Immunization, Division of Emergency and Humanitarian Action and the Division of Emerging and other Communicable Diseases Surveillance and Control) and the United Nations Children’s Fund (UNICEF Programme Division, New York, USA and UNICEF Supply Division, Copenhagen Denmark). It is also the adopted practice of the International federation of the Red Cross and Red Crescent Societies in its operations. WHO/EPI/LHIS/97.04 REV.1

Price has constrained demand for the A-D syringe which now costs \$US .077 against \$US .040 for a typical standard disposable syringe on the international market. In 2000-2001, simplified versions of the A-D syringe will enter the market at significantly lower prices and efforts are being made to transfer A-D technology<sup>5</sup> from two or more sources of intellectual property to five large developing countries.



Safety boxes are designed to contain 100-200 A-D syringes at a cost per syringe disposed of \$US 0.006 to \$US 0.01. These boxes are supplied by UNICEF to all countries ordering syringes for immunization services and they are flat packed for easy distribution to the field.

### 3.1.3 Prospects

For as long as multi-dose vials of vaccine continue to be used, the A-D syringe is likely to remain the injection device of choice for routine immunizations.

**UNICEF-WHO Policy;** A programme of implementation of A-D syringes in immunization has been agreed between WHO and UNICEF<sup>6</sup>:

- ◆ The reuse of standard single-use disposable syringes and needles places the general public at high risk of disease and death.
- ◆ The auto-disable syringe, which is now widely available at low cost, presents the lowest risk of person-to-person transmission of bloodborne pathogens because it cannot be reused. The auto-disable syringe is the equipment of choice for administering vaccines, both in routine immunization and mass campaigns.
- ◆ "Safety boxes", puncture proof containers for collecting and disposing of used disposable and auto-disable syringes, needles and other injection materials reduce the risk posed to health staff and the general public by contaminated needles and syringes.
- ◆ WHO and UNICEF reaffirm the current policy that auto-disable syringes, vaccine and safety boxes should continue to be supplied as a "bundle" for all elective and emergency campaigns.
- ◆ UNICEF reaffirms its current policy that UNICEF's own programme funds cannot be used to procure standard disposable syringes for any immunization purpose.

<sup>5</sup> "Auto-disable syringes for immunization: issues in technology transfer" Lloyd J., Milstien Dr J.: WHO Bulletin: Issue 12, vol. 77, 1999.

<sup>6</sup> "WHO-UNICEF policy statement on the use of auto-disable syringes in immunization services", Draft in process of clearance October 1999.

- ◆ UNICEF also procures supplies and equipment as a service to governments and other organizations, a system known as procurement services. UNICEF hereby announces that as of January 1, 2001 no procurement service contracts for standard disposable syringes will be entered into.
- ◆ WHO and UNICEF urge that by the end of 2001 all countries should use only auto-disable syringes or sterilisable syringes. Standard disposable syringes should no longer be used for immunisation.
- ◆ WHO and UNICEF urge that by the end of 2003, all countries should use only auto-disable syringes for immunisation.
- ◆ All partners of immunization services are requested to finance, not only the vaccines, but also the safe administration of vaccines, auto-disable syringes and safe management of waste. Partners should do this by planning and implementing the above strategy, as well as by supporting related training, supervision and sensitisation.

**Other markets:** The development of other markets for the A-D syringe may also improve their availability and reduce their cost. Injectable family planning drugs are beginning to be delivered now by A-D syringe and there may be a market for a high proportion of skin piercing injections provided through primary health care in developing countries.

On the other hand, industrialised country markets are unlikely to develop for the A-D syringe because it does not prevent accidental needle-stick, which is their main preoccupation. To meet this market, a number of different types of 'safety' syringe have reached the market which either automatically, or manually, protect the needle by sheathing after injection. Automatic needle-sheathing syringes are also, effectively auto-disable but they are costly (\$US 0.75 per unit) and bulky to destroy. Manual needle sheathing devices are less costly (approx \$US 0.012-0.025 additional cost per syringe unit) and may enter the A-D syringe specification when price sensitivity no longer constrains the development of the A-D market.

**Quality assurance:** Most A-D syringes are manufactured in industrialised countries where ISO9002, CEN or USFDA provides some assurance of GMP. However, in spite of ISO certification, several manufacturers of A-Ds have demonstrated quality problems which have been reported by the field and by UNICEF Copenhagen. These problems are likely to multiply with new producers in developing countries. WHO plans, therefore, in the next biennium to work on a quality control mechanism for injection devices based on the same principles as the National Regulatory Authorities (NRAs) which control the quality of vaccines.

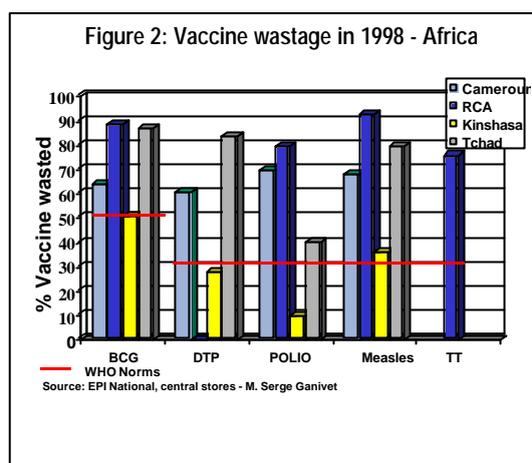
**Needle-free reconstitution for multi-dose vials:**

When A-D syringes are used to inject reconstituted vaccine in multi-dose vials, they are now used in tandem with standard disposable 5ml syringes and needles which are used at the rate of one per vial for the reconstitution process. However, needle-free reconstitution systems exist which permit consecutive pairs of vials of diluent and freeze-dried vaccine to be linked for the reconstitution process without using a syringe and needle. The costs and benefits of these systems will be evaluated in the field and, if satisfactory, introduced into routine and mass immunization.

## 3.2 Mono-dose, pre-filled injection devices

### 3.2.1 Rationale

**Multi-dose vials** have been the standard presentation of almost all vaccine used in developing countries. However, as immunization sessions have become more frequent and more accessible to the population, sessions have become smaller and much vaccine is wasted (around 50%) when partly used vials are discarded after the session. A recent change in global policy<sup>7</sup> permits vials to be used over a month, to control wastage and ensure that when very few children attend sessions, they will not be refused vaccine. Although the evidence in favour of the policy is strong, the safety of this policy remains controversial. Now even the bactericide (Thiomersal), that permits multi-dose vials to be used, is in question. It would appear that the safety of multi-dose vial presentations of vaccine will come under increasing scrutiny in the future.



**Mono-dose presentations** of vaccine eliminate these risks of cross contamination and wastage of vaccine although they cost more and are more bulky to store than multi-dose presentations. If, in addition the vaccine dose is pre-filled into an injection device, the integrity of the vaccine dose is guaranteed up to the moment of use, which is a great safety improvement over manually filling a syringe. Also, the device replaces both the vaccine container and the syringe which offsets most of the device cost. The relative costs depend also on the cost of the vaccine in single and multi-valent format (See Table 2). Mono-dose, pre-filled presentations of new vaccines guarantee safety and they appear today to be economic, although good cost data are not yet available.

Table 2: Comparative system costs of Hepatitis B presentations and injection devices

	Syringe + multi-dose		Syringe + mono-dose		UNIJECT	
	\$US high	\$US low	\$US high	\$US low	\$US high	\$US low
Vaccine	1.175	0.820	1.410	0.950	1.520	1.064
Vaccine waste	0.588	0.164	0.000	0.000	0.000	0.000
Device	0.100	0.084	0.100	0.084	0.170	0.130
Device waste	0.002	0.002	0.002	0.002	0.000	0.000
Cold chain <sup>1</sup>	0.240	0.240	2.400	0.500	0.050	0.000
Disposal	0.045	0.025	0.045	0.025	0.028	0.015
<b>Cost per dose administered</b>	<b>2.150</b>	<b>1.335</b>	<b>3.957</b>	<b>1.561</b>	<b>1.768</b>	<b>1.209</b>

<sup>1</sup> Portion of cold chain costs incurred at peripheral level

Source: Based on device, vaccine and waste costs presented in cost study PATH-MOH Indonesia, 1997.

<sup>7</sup> "The Use of Multi-dose Vaccine Vials in Subsequent Immunization sessions. WHO Policy Statement", WHO/EPI/LHIS/Original: English, October 1999.

### 3.2.2 Status

Pre-filled, mono-dose injection devices, for both liquid and lyophilised vaccines, have been on the US and European market for the last twenty years but they incorporate glass containers for the vaccine and are often more costly than the vaccine that they contain. They also typically occupy more than twenty times the storage volume of ten-dose presentations and twice the volume of single dose vials. However, one new plastic “pouch and needle” device, developed by PATH, USA, with support from USAID, is now marketed by BD Inc. under the tradename UniJect™. This device has been extensively field tested in Bolivia and Indonesia, where health workers found the device easy to use for the injection of tetanus toxoid and where village midwives were able to administer the birth dose of Hepatitis B, thereby raising coverage with this vaccine<sup>8</sup>.



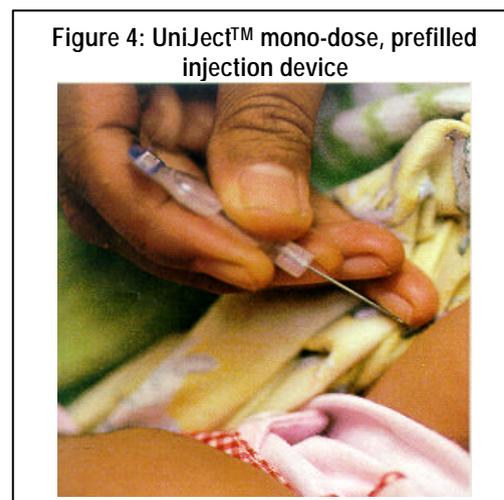
BD and UNICEF are engaged in a project to immunize 20 million women in risk areas for neonatal tetanus using UniJect™. In addition, PATH is working on the application of UniJect™ with multiple partners in studies of the delivery of the injectable contraceptive ‘Cyclofem’. In a study in Brazil, UniJect™ has shown such high levels of safety and user acceptance that the government has declared the device to be suitable for the delivery of all injectable contraceptives.

This device guarantees the integrity and sterility of the vaccine dose up to the moment of use, it generates a volume and weight of waste which is 30% lower than the 2ml syringe and mono-dose vial, it is auto-disable and it occupies less than half the volume of the syringe and vial in distribution. The needle, however, remains a needle-stick hazard.

### 3.2.3 Prospects

Clearly the convenience of UniJect™ facilitates high public health impact in areas which are difficult to reach. But the cost of administering tetanus toxoid with this device rises from around \$US 0.10 to around \$US 0.22 which is likely to keep this presentation as a ‘niche’ market. But when more costly vaccines, such as Hepatitis B or multi-valent vaccines are considered, the presentation is economic as well as safe and convenient.

As new, more costly vaccines are introduced and as current antigens are incorporated within them, mono-dose, pre-filled injection



<sup>8</sup> “Achieving Universal Childhood Immunization with Hepatitis B Vaccine: Policy and Cost Effectiveness Issues”, Prepared for the Ministry of Health Indonesia, PATH, April 1996.

devices such as the UniJect™ are likely to become mainstream presentations. Indonesia has begun to fill Hepatitis vaccine in UniJect™ for distribution to several provinces for routine immunization. Other vaccine manufacturers are investigating filling in mono-dose prefilled devices which require compatibility testing for long term storage in plastic.

### 3.3 Needle-free injections

#### 3.3.1 Rationale

Non-parenteral routes of vaccine administration have less risk of transmission of blood borne pathogens than that associated with injections. But, with the exception of oral polio which has a limited horizon, most vaccines emerging in the first decade of the millenium will be injected. Needle-free injection delivers the dose of vaccine at high velocity into the dermal and subcutaneous layers without the penetration of a needle. Needle-free injectors eliminate the risks of accidental needle-stick after injection and during the process of waste management. They also generate the least waste. Technologies are in development for both multi-dose and mono-dose presentations of vaccine.

**Multi-dose** injectors draw vaccine from multi-dose vials of vaccine and are able to give sequential injections rapidly, with no risk of accidental needle-stick, with no sharps waste burden and at lowest cost per dose delivered.

**Mono-dose** injectors draw vaccine from single-dose container of vaccine which are either an integral part of an entirely disposable injector, or they are cartridges that fit inside a reusable injection device. In both cases the fluid pathway of the injector is entirely disposable and non-resuable.

#### 3.3.2 Status

Current models of **multi-dose** injectors have been demonstrated by animal and human tests to be a potential source of cross-injection with blood-borne pathogens and are no longer recommended. Fortunately, the testing appears to have revealed the contamination pathway and new and modified multi-dose injectors are now being tested.

Several models of **mono-dose** injector are available on the market, including both the entirely disposable type and the cartridge type. The main constraint for immunization services in developing countries is that new vaccine products must be regulated for storage in these devices. If a standard cartridge is established, this is not a serious obstacle and the cost per shot could be low because the cost of the injector is amortised into it's lifetime. If, however, a proprietary cartridge is to be developed for each injector, or if the entirely disposable type is to be used, the costs will be very high (\$US 1-1.50 per shot for the device only) and it is not clear how

Figure 5: Multi-dose needle-free injector



Figure 6: Mono-dose needle-free injectors



such diversity could be handled, either by the vaccine industry or by the public sector consumers for the developing countries.

For this reason, PMC, France and Am-O-Jet, USA are collaborating on a new initiative to advance a standard, low-cost cartridge (“Immule”) which would be available to all vaccine manufacturers and would fit in a wide range of reusable needle-free injection devices. Such a delivery system, while not self-contained and requiring the wide availability of well maintained injection guns, could be both economic and practical for use in many developing country settings.

### 3.3.3 Prospects

The **multi-dose** needle free injector would lower the cost and raise the safety and speed of injectable immunization campaigns, if it can be demonstrated to be safe. For this reason a very high priority is placed on the acceleration of the necessary development to make such an injector available as soon as possible.

The **mono-dose “Immule”** system has potential to be used both for mass immunization where thousands of injections per day are to be given with heavy-duty reusable injection devices. With compact, handheld devices that last for around 25,000 shots maintenance-free and are then discarded, Immule could also be used for routine immunization where only a few doses per day are given. It is not clear at this stage whether the costs, logistics and safety benefits will weigh in favour of mono-dose prefilled needles or in favour of the mono-dose needle-free injection systems.

The time required to develop, validate, register and gain acceptance of (by vaccine manufacturers and the international health care community) new delivery systems can be seven to ten years or more. It is possible that other needle-free technologies currently in the development pipeline will compete with pre-filled, unit dose jet injection for precedence in public health strategies to reduce injections. These technologies involve transcutaneous, transdermal and transmucosal approaches.

## 3.4 *Point-of-use sharps processing technologies*

The recommendation of WHO for immunization services is that syringes and needles should be destroyed as soon after the injection has been given and as close to the place where the injection has been given as possible. Destruction by incineration, with acceptable environmental standards, to meet this recommendation is rarely, if ever, possible. So, if syringes and needles must be stored and carried to the point of destruction it is evident that the hazards of sharps and infection should be minimised.

### 3.4.1 Rationale

The hazards of storing and transporting infected syringes and needles to the point of final disposal can be reduced by “de-fanging” (separating, encapsulating or destroying the needle), disinfection and compaction. Once “de-fanged”, the sharps are no longer a hazard for accidental needle-stick. Once disinfected, cross infection is less likely. Once compacted the process of storage and transport becomes more feasible.

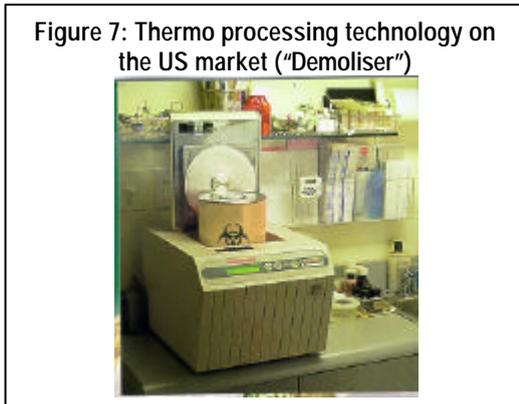
### 3.4.2 Status

A number of technologies exist or are in the process of development.

**Disinfectants** are of course available but they are corrosive, costly and have comparatively narrow spectra of inactivation. New, liposome-based de-contaminants

hold some promise as very low cost, highly effective and entirely safe products for use in developing countries and, with the necessary research and development, could be made available.

**Thermo-processing**, or melting, is available in the US and could, with some modification, be made available wherever electricity supplies are available. Thermo-processing disinfects, compacts and encapsulates needles within the plastic of the syringes. The resulting cake may be discarded in domestic waste, recycled or incinerated.



**Needle-destroyers** are available and these either destroy the needle entirely using an electrical current, or they cut the needle and hub away from the syringe for separate disposal by burying. The remaining syringes are thus less of a hazard to disinfect and transport. Some 'long-life' devices are transportable but not easily portable while other 'short life devices' are designed to be supplied, carried and discarded with the sharps safety box. Standard disposable syringes and newer A-D syringes with separate needles can be de-fanged by one-handed removal of the needle into a sealed container with a V-slot opening.

**Plasma-melting** and **small scale incineration** are, today, technologies which do not appear practical or economic in clinics, but could serve as district-based waste destruction points. Plasma-melting requires electricity but has the important advantage over small scale incineration that there is no emission-to-atmosphere hazard. This technology is currently being developed for use at district level.

### 3.4.3 Prospects

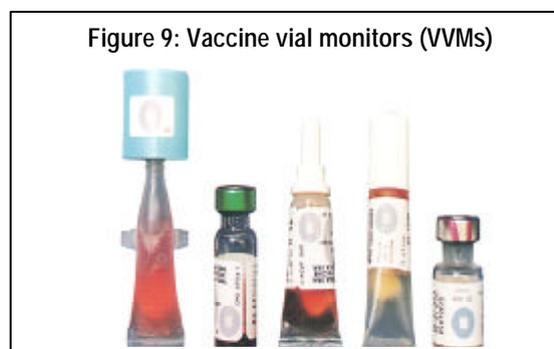
Until a practical technology becomes available for the final destruction of syringes and needles at the point of use in developing countries, waste processing technologies will remain critically important to eliminate the hazards of storage and transport. Technologies for final disposal will have to meet stringent environmental standards to be acceptable in the future. This suggests that greater investment and higher technologies will be needed to achieve these standards than are currently available at district level.

### 3.5 *Thermostable vaccines and Vaccine Vial Monitors*

Vaccine products are regulated to be stored and transported in refrigeration, even though certain new mono-valent products are already very heat stable and other multi-valent products contain some very stable antigens. To conform with this strict

regulation, a cold chain system has been established all over the world which increases the cost of immunization by around 14%. This figure will rise if new, mono-dose vaccine products are to remain in the cold chain. Vaccine vial monitors (VVMs) now enable health workers and managers to react appropriately to weaknesses in the cold chain and they allow flexibility for vaccines to be used in difficult circumstances beyond the reach of ice and refrigeration. But they do not allow for the elimination of the cold chain.

Technology now exists to make vaccines that can be stored and transported routinely at tropical room temperatures or in freezing temperate climates. Extreme exposure can be monitored by VVMs. New, multi-valent vaccines stabilised with this technology would be regulated for shelf-life storage at temperate or tropical (30C) room temperatures.



### 3.5.1 Rationale

Vaccine distribution without a cold chain would considerably simplify the delivery system and make it easier to integrate with drug distribution in developing countries. Sugar-glass drying technology now exists to make vaccines that can be stored and transported routinely at tropical room temperatures or in freezing climates. Extremes can be monitored by VVMs. New, multi-valent vaccines stabilised with this technology would be regulated for shelf-life storage at temperate or tropical room temperatures.

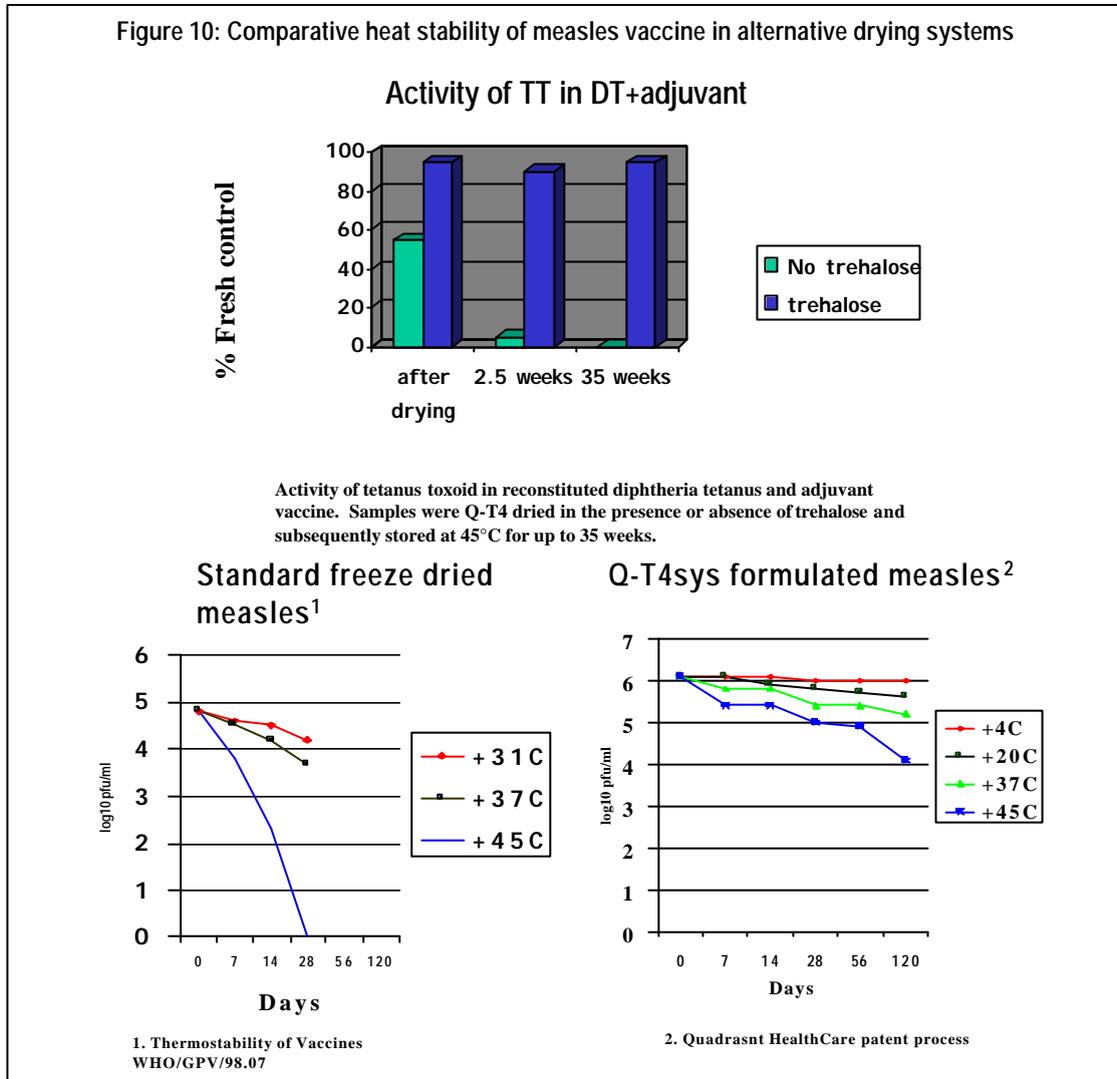
Clearly, while some vaccines are still regulated for storage in refrigeration, the cold chain must remain for those vaccines. But many multi-valent vaccines now incorporate both 'new' and traditional bacterial vaccines, such as DPT. Once all vaccines have been stabilized, refrigerated equipment and the associated maintenance is no longer needed, saving approximately \$US 200 million globally each year.

**Why sugar glass?**<sup>9</sup> Research studies conducted in industry have shown that key to a vaccine's high temperature stability is the long-term stabilizing ability of certain sugars. The first hint of the potential of sugars as vaccine stabilisers was given by a number of living organisms, the cryptobionts. These organisms have the attribute of drying out completely under stressful physicochemical conditions, then regaining full metabolic activity when subsequently exposed to water. The unifying feature between cryptobionts was found to be the presence, in high concentrations, of the simple yet unique disaccharide trehalose. Trehalose is amongst the most chemically unreactive and stable of sugars. The two glucose moieties are joined through their reducing carbons and the resulting  $\alpha$ -1,1 glycosidic bond has a very low energy of less than 1kcal/mol. This makes trehalose not only non-reducing but very stable to hydrolysis.

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<sup>9</sup> "Advances in parenteral delivery of vaccines as solids may revolutionise immunization campaigns worldwide" GENETIC ENGINEERING NEWS February 15 1998

Other non-reducing sugars have also been used effectively for preservation of biological materials.



A sugar-based drying and stabilizing technology has already been developed and applied to a number of vaccine antigens. For example, in a study done with dried measles vaccine, researchers showed that the vaccine stabilized with trehalose suffered no loss of activity after two months at room temperature compared to a commercial freeze-dried measles vaccine which lost over 90% of the original titre in the same amount of time. In another study, stability of a trehalose-dried combination of diphtheria, tetanus and acellular pertussis antigens (DTaP) adsorbed to aluminium hydroxide adjuvant was compared with the conventional vaccine. Stored at 60°C for up to 12 weeks, the trehalose-dried DTaP antigens and adjuvant were shown to be biologically and chemically unaltered. Pre-clinical investigations have demonstrated the immunogenicity and potency of the trehalose-dried vaccine candidate.

Only live polio vaccine failed to dry<sup>10</sup> successfully due to the complex molecular structure of the virus which prevents trehalose from full penetration.

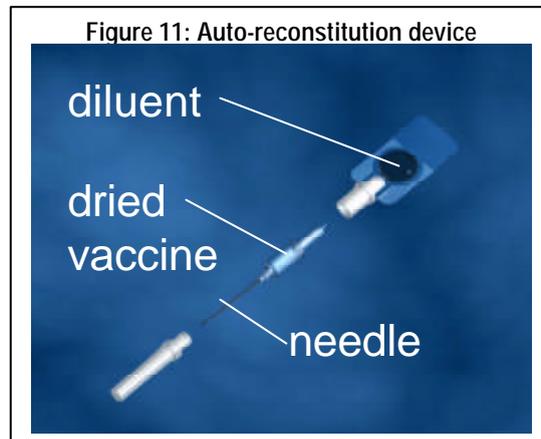
### 3.5.2 Status

**Intellectual property** in sugar-glass drying processes for vaccines is in the hands of a small number of companies and individuals including:

- ◆ Durer Chemical Corp. USA
- ◆ Quadrant Health Care, UK
- ◆ CSIR, Australia
- ◆ Universal Preservation Technologies, USA
- ◆ B.Roser, Anglia Research, UK

These sources of IP have been used by the vaccine industry to develop sugar-glass dried versions of their products but, although the results have been encouraging, the high cost of regulation and the lack of a sure market has prevented any sugar-dried vaccine product from reaching licensure.

**Automatic reconstitution:** To enable sugar-dried vaccine to be administered as a liquid, work is in progress to develop an automatic reconstitution of sugar-dried vaccine within a type of needle hub which can be fitted to a standard syringe or a mono-dose plastic reservoir such as the UniJect™. The vaccine, dried as a foam, reconstitutes during the process of the injection, as the syringe or pouch forces diluent through the needle 'hub' and down the needle.



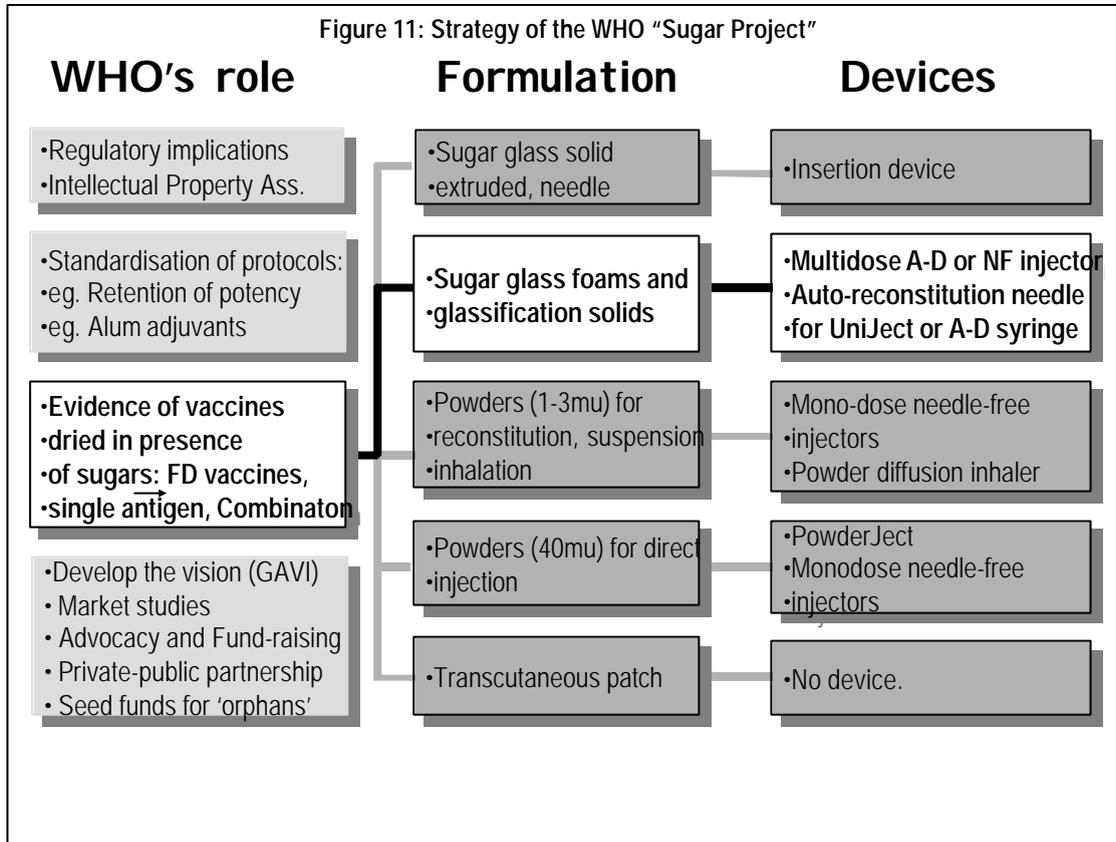
**Needle-free systems for dried vaccines:** Two parenteral systems have been proposed for the delivery of sugar-glass dried vaccines. The first requires that the vaccine is spray dried in the form of a fine powder (1-3 microns) and suspended in a non-aqueous liquid to be injected through needles or under pressure as a liquid jet-stream. The second system, named PowderJect™, is designed to deliver powder and could inject particles of sugar-dried vaccine (approx 40 micron particles) at 850 m/s directly into the epidermis. In this case, the vaccine would be stored between two diaphragms in a removeable or integral capsule within the injector body. Both systems require research and development, but the PowderJect™ has already reached the market with anaesthetic products and has been successfully tested with vaccines.

### 3.5.3 Prospects

Until now, vaccine manufacturers have been reluctant to exploit the sugar-glass drying technology because the market for stabilised vaccine products do not exist in the industrialised countries and the commitment of clients for the developing world is

<sup>10</sup> "Development of a dry and thermostable oral polio vaccine", RIVM-Kampinga et al., WHO Funded Research 1993.

not sure. This uncertainty is unlikely to be bridged by a single decision or a single expression of commitment. Nevertheless, WHO is launching the ‘Sugar Project’ on January 1<sup>st</sup> 2000 following the strategy outline in Figure 11.



**Licensed, sugar-glass dried vaccine products:** The most advanced path towards the vision of thermostable vaccines is emphasised in the strategy diagram above. This path represents a priority for the partners of the vision because it has the best chance for early progress and could establish a ‘prevalent’ vaccine delivery technology during the next ten years. WHO is collaborating with the Programme for Appropriate Technology in Health (PATH), in this course of development which started in 1999, funded by the The USAID-supported Healthtech program and the Bill and Melinda Gates Foundation Children’s Vaccine Programme. The project will proceed in four steps, each step developing a licensed product:

- ◆ First, demonstrate that measles vaccine can be more economically and rapidly produced using these drying methods than the current freeze-dried vaccine<sup>11</sup>, factors critical to global measles control and elimination;

<sup>11</sup> The Sugar Project working group, which met in Geneva in March 1999, noted that alternative, air or vacuum drying processes, that create a sugar-glass foam, are three times quicker than freeze drying although they can be conducted without refrigeration, in the same equipment. The resulting dried vaccine product re-constitutes several times faster than freeze dried vaccine and is at least four times more heat stable.

- ◆ Second, demonstrate that measles vaccine can also be sugar-dried and presented in a pre-filled, mono-dose injection device that automatically reconstitutes the dried vaccine during the process of injection. This product has the potential to raise routine coverage with measles vaccine and to assure safety;
- ◆ Third, develop a sugar-glass dried multi-valent vaccine in an auto-reconstitution, mono-dose, pre-filled needle and demonstrate shelf life at tropical room temperature;
- ◆ Fourth, develop a sugar-glass dried multi-valent vaccine in a cartridge to be used, either as a powder for direct powder injection or as a non-aqueous suspension for liquid needle-free injection.

**Sugar-glass needle:** Possibly the most radical and ambitious solution to ‘needle-free’ parenteral delivery of sugar-glass dried vaccine is the concept of the sugar needle. The concept, as yet only superficially tested, suggests that it is possible to fabricate a sugar glass as a solid needle, so that the vaccine itself is the needle. Once inserted the ‘needle’ then quickly dissolves leaving only the packaging and the insertion device behind. The concept remains both controversial and tentative. It is claimed that solid sectors of the needle may be dedicated to different antigens and that the engineering of the needle surface may permit dissolution in the body at controllable rates.

A second, related concept is that of a **hypodermic needle constructed of a bio-degradable material**, possibly even a sugar, which would achieve the safety advantages of needle-free injection with a simpler, more conventional technology. This concept is not yet on the horizon but should be pursued so that the safety of needle-based injection systems can be maximised.

## 4 Timetable & milestones

Each technology passes through four phases of research and development, product launch, market development and post market monitoring.

Activity	00	01	02	03	04	05	06	07	08	09	10
<b>1. Safer multi-dose vaccine delivery</b>											
◆ A-D & safety boxes only for mass immunization											
◆ A-D or sterilizeables & safety boxes for routine, <b>no</b> disposable syringes											Unlikely that Multi-dose vials will still be used.
◆ Only A-D for routine, unless sterilization monitored											
◆ Needle-free manual re-constitution devices											
◆ Re-introduction of multi-dose, re-usable needle-free injectors for campaigns											
◆ Thermo-processing											
◆ Needle destructors											
◆ Small scale incinerators											
<b>2. Mono-dose, pre-filled injection devices</b>											
◆ Tetanus toxoid and monovalent HepB vaccine in mono-dose, pre-filled devices											
◆ Liquid pentavalent vaccine in mono-dose, pre-filled devices											
◆ Development of mono-dose needle-free injectors for all immunizations											
<b>3. Thermostable vaccines distributed with drugs</b>											
◆ Development and introduction of a sugar-glass multi-dose measles vaccine											
◆ Sugar-glass, measles vaccine in auto-reconstitution, mono-dose, pre-filled needle											
◆ Sugar-glass, multi-valent vaccine in auto-reconstitution, mono-dose, pre-filled needle											
◆ Sugar-glass, multi-valent vaccine in mono-dose, needle-free injectors											

Key:



Research & development



Product introduction



Market development



Post market monitoring

#### **4.1 Partners & Funding**

The current partners in this endeavour, and the co-originators of this White Paper are WHO, UNICEF and PATH. WHO and UNICEF have, over the last 20 years been instrumental in broad introduction of vaccine delivery technology, while PATH with the backing of USAID, has been the most prominent and successful development agent for new technologies. The future partners in this endeavour should be those of the Global Alliance of Vaccines and Immunization (GAVI). It is proposed that this endeavour will be supported as a blueprint of future immunization technology by the Alliance.