



**STEERING GROUP ON THE DEVELOPMENT OF JET INJECTION
FOR IMMUNIZATION**

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1. INTRODUCTION

1.1. *Why jet injection?*

Immunization programs world-wide face problems and opportunities for the future which, WHO believes, may be significantly altered by the advent of new vaccines and new injection technologies. While alternative immunization technologies like nucleic acid vaccines and oral vaccines may ultimately prove safe, effective and practical means to administer any or all of these antigens, it is equally important to rethink how parenteral immunization - a “proven” concept - might also be improved to do so. Jet injection offers the potential for safety, economy and convenience which will earn it a market share in the injection device industry both for pharmaceuticals and for vaccines.

In both industrialised and developing countries injection safety is a major and increasing concern to the public, the health community and to the agencies. In industrialised countries, the main issue is the prevalence and consequences of accidental needlestick. While this is also a problem in developing countries, the main issue in these countries is the reuse and resale of disposable syringes.

Globally, injections for immunization are projected to rise steeply. In industrialised countries, this is due to a proliferation of new antigens and, in developing countries, it is due to the advent of mass immunization for disease control and elimination. Popular demand for immunizations is especially vulnerable to risks and consequences of unsafe injections, to accidental needlestick and the reuse of contaminated injection equipment.

1.2. *A new paradigm...*

Future immunization services will take full advantage of each contact with the child to give a large number of different antigens. Injection devices that can administer multiple vaccines parenterally at one visit relatively painlessly, using (safe, disposable, standardised) single dose vaccine containers containing heat stable vaccines, would permit an alternative paradigm to be embraced for immunization.

Jet injection technology offers the means to deliver vaccines with no waste, with “zero-risk” injection technology and with the minimum of pain. Powder injection could eliminate the risk of cross infection completely. Multi-dose vials of liquid vaccine will continue to be a convenient way of dispensing liquid vaccines in mass immunization. But in the longer term single dose presentations, standardised for injection devices, may replace them in routine immunization in developing countries, as they have largely done in industrialised countries.

In this case, it would not be necessary to resort to vaccine combinations as the sole solution to multiple and increasing numbers of antigens. Certainly some, standardised combinations may be adopted internationally, as they are today. But the profusion of overlapping combinations which threatens confusion in industrialised countries would be

avoided and the vaccine manufacturers in developing countries would be assured a place in the market.

Jet injection has an important place in these scenarios for the future. But also in the short term, the multi-dose jet injector must be made safe for mass immunization. Current tests and trials suggest that this will be possible by the end of 1998.

The active and transparent collaboration of the vaccine and the injection device industry will be needed to reach both the short term and the long term objectives. To invest in the necessary changes, these industries will demand clear signals from all sectors of public health which use injections, not just immunization. This vital process of collaboration for development is the prime purpose of this Steering Group convened by WHO.

1.3. Terms of reference of the Steering Group

Goal of the group	To promote the development of jet injection as a safe, less painful, rapid and cost-effective means of administering current and future vaccines world wide.
Objectives	<ol style="list-style-type: none">1. In the short term (by 1998), to make available safe, reusable, multi-dose jet injection for routine and mass immunization.2. In the medium term, to facilitate the development of disposable, single-dose jet injection of liquid vaccines.3. In the long term, to facilitate the development of jet injection of powdered vaccines without reconstitution with liquid.
Working method	<p>To act primarily as an advocacy and action group, identifying tasks to be done, obstacles to be overcome, setting strategies and pursuing their implementation to:</p> <ol style="list-style-type: none">1. develop and maintain standard performance requirements for jet injection technologies together with the procedures for qualifying new products to meet those standards,2. review jet injection devices at all stages of development, assisting in the progress of selected devices towards the market by qualification tests in the laboratory and the field,3. liaise with the necessary partners (including the vaccine and device industries) to encourage the development of standardised integrated systems of vaccine delivery.

2. THE PROBLEM

2.1. Developing countries

Studies in Central and East Africa have shown that routine immunizations account for respectively 17% and 22% of all injections given. Although this is a small percentage, popular acceptance of immunization is particularly sensitive to safety issues and this sensitivity is growing with awareness of HIV transmission globally.

2.1.1. Unsafe injections

The sub-committee of the Technical Network on Logistics in Health reported at their meeting in Geneva in November 1996¹ that unsafe injection practices are widely reported in the immunization programmes of developing countries and that the primary problems were the frequent reuse of disposable syringes and the failure to dispose of contaminated needles and syringes. Countries using sterilizeable syringes are also widely reported to be unable to assure that steam sterilizers are used correctly or, in certain countries, to use them at all.

Although there is a wealth of epidemiological evidence from industrialised countries on the spread of Hepatitis due to accidental needlestick and the shared use of syringes and needles, there is little direct documentation from developing countries of the extent to which unsterile needles and syringes contribute to HBV and HIV infection. These infections are asymptomatic, the incubation periods are long and few studies have been targetted at this issue. However, published model-based estimates of the risks associated with reuse of syringes and needles put the figure of Hepatitis infections as high as 51 per 100,000 fully immunized children receiving injections from syringes used twice. (See figure 1).

Figure : 1 Cases of disease associated with the re-use of unsterile needles²

	Infants under 1 year per 100,000 fully immunized		Women of childbearing age per 100,000 fully immunized	
	1 reuse	4 reuses	1 reuse	4 reuses
HIV	0.3 to 51	0.4 to 81	1.3 to 140	3.6 to 470
Hepatitis B	52 to 980	210 to 3740	63 to 600	250 to 2280
Rates based on low and high rates of HbsAg prevalence in women and a low rates (0.1%) and high rates (20%) of HIV prevalence in the population				

¹ TECHNET Sub Committee Meeting on the Safety of Injections, WHO, Geneva 29/10 to 1/11/1996

² "Model-Based Estimates of the Risk of Human Immunodeficiency Virus and Hepatitis B Virus Transmission through unsafe injections", B. Aylward et al.. International Journal of Epidemiology, Vol. 24, No 2, 1995.



In this picture of an immunization session in an African country, seven multi-dose vials of vaccine are in use and three used syringes are available.

Reuse occurs both within the health sector and, through resale or through improper disposal, outside the health sector. The essential problems stem from the re-usability of standard disposable syringes, the flexibility of syringes with separate needles and reluctance of societies to dispose of scarce commodities.

Even where disposal occurs, syringes are rarely burned properly and the disposal process is not supervised. Accidental needlestick is consequently a real danger to the community as well as to health staff.

2.1.2. Demands of mass immunization

To compound the problem of injection safety in routine immunization, standard disposable syringes have been supplied in very large quantities for mass immunization in both elective and in emergency settings. These syringes are often supplied to countries which are neither prepared nor equipped to dispose of them after a single use.

In settings where injection materials are generally scarce, unsafe injection and disposal practices are widely tolerated and syringe, once used for mass immunization, are then passed on for other uses.

They are also, in some cases, diverted for other uses and even other markets before they reach the field in a mass immunization campaign. In this case, there remain insufficient syringes for the campaign, provoking further reuse of contaminated syringes.

In addition to the dangers they provoke, syringes and needles are inferior to jet injectors in mass immunization operations. Several trained health staff are required at each post to prepare and use the syringes fast enough to maintain the required rates of immunization. Where staff are scarce, immunization rates are slow and this impairs coverage of the target population.

2.1.3. Rising costs of safety

When the Expanded Programme of Immunization was launched twenty three years ago, more than half the injections given for immunization were administered by sterilizable syringe and needle. Although the sterilization process was arduous, costly and not always reliable, the cost of these injections was around 1 cent US per injection³. Traditional jet injectors, which were used for mass immunization and which are entirely reusable, cost

³ In immunization sessions of 50 injections, including sterilization but not including labour or disposal

more per injection than sterilizeable syringes but less than disposable syringes and needles.

Concerns about safety have caused most countries to turn to standard disposable syringes (4 cents per syringe and needle). Even where sterilizeable syringes continue to be used for routine immunization, disposables are used in mass immunization and in the curative service. Mixed sterilizeable and disposable policies have created confusion in many countries.

In the last five years, increasing concern for safety has driven the introduction of auto-destruct syringes in place of standard, disposable syringes to prevent reuse. This has increased the cost per syringe to 8.8 cents. The prospect for the near future is no better than 6 cents per auto-destruct syringe. In addition to the cost of the syringe, the cost of disposal at the point of use is estimated to be about 2 cents per injection (safety-sharps boxes and incineration). Thus, the total cost per 'safe' injection is now around 10 cents.

The premium paid for safety is therefore more than double the cost of the standard disposable syringe, yet protection against accidental needle-stick has not yet been tackled at source. Multi-dose jet injectors are now undergoing modification to increase their safety which will incorporate disposable parts costing as much as 6 cents more per shot than before.

2.1.4. Impractical vaccine logistics

The vaccine presentation has to be considered with injection devices because vaccine presentation may help or hinder the process of administration.

Freeze dried vaccines, such as measles, BCG and yellow fever must be reconstituted to be injected by syringe and needle, a process which slows down the rate at which immunizations can be given and which increases the risk of error. Once reconstituted, these vaccines are highly heat labile and, if kept too long, not only lose their potency but can become dangerously contaminated. In routine use, levels of wastage commonly exceed 40% while in mass immunization the main problem is the staff-intensive, slow rate at which they can be administered.

Freeze drying, while creating highly stable vaccines in powder form, does not protect the vaccines in use and limits rate of production to the capacity of the freeze drying equipment. The cost of this equipment is a significant proportion of the cost of making the vaccine.

Multi-dose presentation of vaccines is appropriate for mass immunization because the vaccine is utilized efficiently and the cost is therefore low. However, when used in small routine immunization sessions and discarded the same day, the wastage is very high. The current solution to this problem is to keep vaccines (except reconstituted vaccines) for a longer period, relying heavily on the bactericides in the formulation. Western Europe, the United States and some other industrialised countries have adopted single dose presentation for market reasons including safety.

Barriers prevent the single dose presentation from being introduced in developing countries. These include increased vaccine cost, lower rates of production and an increase in the volume of packed vaccine to be stored in the cold chain.

2.2. Industrialised countries

2.2.1. Risk of accidental needlestick

Accidental needlestick injuries are estimated to occur at the rate of 6.9 to every 100,000 disposable syringes in the United States⁴. Blood borne pathogens are transmitted at the rate of 30% when the needle has been contaminated by a carrier of Hepatitis B and at the rate of 0.3% when the needle has been contaminated by an HIV positive individual. Health workers have a 2 to 10 fold risk of Hepatitis B infection compared to the rest of the population. 50% to 80% of parenteral drug users have been infected by blood-borne pathogens such as Hepatitis B and HIV due to the shared use of needles and syringes. The annual cost burden of each needlestick injury has been estimated to be \$US 405 in 1990, equivalent to about 15 cents US⁵ per syringe and needle.

While jet injectors, in some cases, produce disposable waste after each shot, this waste is not 'sharp'.

2.2.2. Need to reduce pain

Pain provoked by needle injection has been shown in a number of studies to be a significant factor in rejection of injections, particularly in children under sixteen. As childhood immunization schedules in the United States are now heavily loaded, multiple sequential injections must be given in the same immunization session in different injection sites. This is both painful for the child and distressing to the parent or guardian.

It is now felt by many immunization managers that neither children nor their parents will tolerate more than four injections with needles and syringes at one contact. Some countries will not permit more than two. The main factor for this is fear of injections due to pain. An important contributing factor to the level of pain is the volume of the standard 0.5ml dose of vaccine which was chosen to assure that an accurate dose could be drawn by a 2ml or 3ml syringe. However, when metered automatically by jet injection, the standard dose could be reduced to 0.1ml, thereby greatly reducing pain.

Jet injectors have showed lower thresholds of pain in tests with both subcutaneous and intradermal injections and with both children and adults. Lower levels of pain would permit multiple shots to be given at different, but adjacent injection sites, simultaneously. Weston, UK have demonstrated a jet injector which will give multiple injections simultaneously in this way.

⁴ Jagger, New England Journal of Medicine, 1988;319:284-8

⁵ This figure does not factor in Hepatitis immunization of health staff in the US which may be reducing the cost of injury but which costs around \$US400 million.

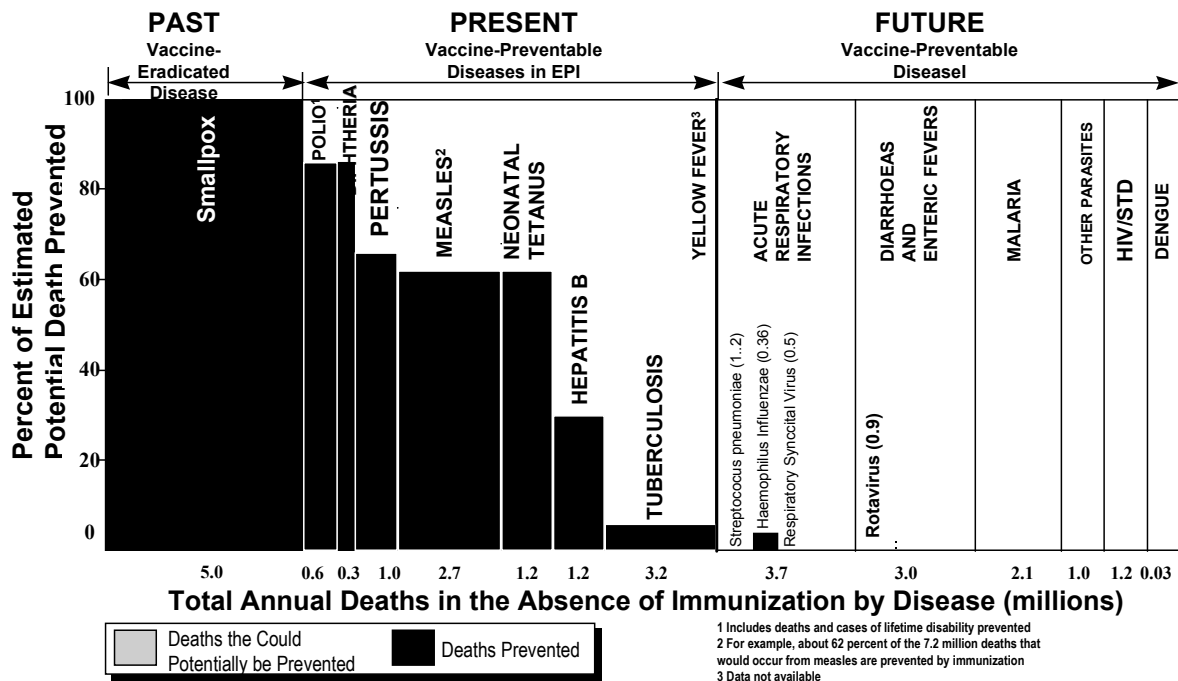
Vaccines combinations would be less necessary if antigens could be administered individually and the process of regulatory testing would be shorter. The present ‘open market’ for combination vaccines is already creating confusion in the immunization services of the United States.

3. THE VISION

3.1. Evolution of the immunization market

The immunization market is likely to expand spectacularly in the early part of the next century. Disease control and elimination strategies target large sectors of the world population and an ever increasing number of vaccines promise to reduce the global disease burden dramatically (See Figure 2).

Figure 2: Potential of Immunization to Prevent Death⁶



The annual number of injections given for immunization now exceeds one billion. Becton Dickinson, the largest producer of syringes, estimates the immunization market at 1.2 to 1.6 billion per year, excluding China and India. Increasing population, the advent of mass immunization for disease eradication and the arrival of new vaccines is likely to raise this figure by four to five times by the year 2005⁷.

⁶ Source: WHO/GPV adapted by the Programme for Appropriate Health Technology (PATH) USA

⁷ The immunization market is known to be approximately one tenth of the total, global market for injections including the curative sector.

3.1.1. Immunizations in the “High income” economies

In 1994, the population of the 25 “high income economies” of the world⁸ was 850 million, or about 15% of the world population. The annual birth cohort of this population was around 12 million and, assuming a level of injectable immunizations given in the United States, about 180 million injections were given for immunization. At least ten times this figure would approximate the number of injections given for all purposes to the whole population of these countries.

The IOM⁹ estimate for North America, Europe and Japan put this figure of injections for immunization higher at 211 million.

3.1.2. Developing countries

Routine immunization of children under 1 year and TT immunization of women generated a little under 800 million injections in the developing world last year. This level of injections for routine immunization is likely to rise to 2.3 billion, taking account of only today’s vaccines.

In addition to routine immunization, emergency disease outbreak control operations against meningitis and diphtheria have given more than 240 million injections in the same year.

Injection type / vaccine	Live births multiplier*	Global % coverage DCs 1996	No. injections x 1000
Intra-muscular, adult			94193
Tetanus Toxoid	1.5	48	94193
Intra-muscular, child			404246
DPT	3	81	317902
HepB	3	22	86344
Subcutaneous / child			132132
Measles	1	79	103351
Hib	1	0	0
Yellow fever	1	22	28781
Intra-dermal, child			162222
BCG at birth	1	88	115125
BCG booster	0.6	60	47097
GLOBAL DC TOTAL			792793
* Global live births in DCs 1996 millions			130824

Towards the end of the century the process of measles eradication is likely to begin. Elective mass immunization will target about 6.7 billion children under 15 years by the year 2005. By 1999 an estimated 222 million supplementary doses of tetanus toxoid will have been administered to 74 million women in neonatal tetanus elimination operations.

3.2. New vaccines, more injections

3.2.1. Number of antigens is increasing

The number of antigens routinely administered in the industrialised countries is increasing rapidly. In the United States alone the number of combination vaccines has risen from 5 in 1995 to 23 confirmed or expected new vaccines by the end of this year. WHO anticipates seven new vaccines will be available for childhood immunization in developing countries by the year 2005, of which six will be injectable.

⁸ World Development Report 1996, World Bank

⁹ Children’s Vaccine Initiative (CVI) - Achieving the Vision 1990

Yellow Fever	Injectable	All countries
HIB	Injectable	Endemic
DPT/HB	Injectable	All countries
Rotavirus	Oral	All countries
Pneumococcal	Injectable	Endemic
Diphtheria/Typhoid	Injectable	All countries

The parenteral route of administration, while being invasive and therefore more problematic than oral or nasal routes, is likely to remain as a reliable way to deliver vaccines in the future.

In addition to the vaccines of high priority for developing countries there are eighteen new or combined antigens expected to enter the global market soon.

3.2.2. More simultaneous injections

This increase in the number of antigens is unlikely to be accompanied, at least in developing countries, by an increase in the number of immunization contacts. Neither will parents in the industrialised countries be likely to accept many more visits for immunization. In this case, two alternative scenarios present themselves:

- combination vaccines will be the key to minimising the number of simultaneous injections but:
 - combinations will have to be standardised, at least for developing countries, to avoid operational confusion in immunization services
 - serious problems will present themselves where national vaccine manufacturers will be capable of producing some components, but not all components of a standard combination vaccine
 - combinations will be minimised to certain commonly available vaccines and other antigens will be systematically presented in single-antigen format but:
 - simultaneous injections at the same session will need to be made less painful by reducing the volume of the dose and/or changing the means of injection

3.3. *Stable vaccines - elimination of the cold chain*

New vaccines are likely to be considerably more heat stable than the traditional vaccines used today. Recombinant vaccines, such as Hepatitis B, are already among the most stable vaccines available and new powder presentations offer the prospect of entirely heat stable vaccines in the future. The impact on injections of progressively removing vaccines from the cold chain (system of refrigerated storage and transport) will be considerable, both for industrialised and for developing countries:

3.3.1. Use of the postal system

In industrialised countries with widespread private medical services such as the United States, the postal system might be used to distribute vaccine.

3.3.2. Injections given by less trained personnel

In developing countries high immunization coverage depends on the service reaching out to the most remote areas and the most unde-served populations. For example, the success of polio eradication is due to some extent on the administration of the vaccine by large numbers of volunteers. Midwives are being taught to administer tetanus toxoid using

simple single dose injection devices (Uniject) to raise routine protection against neonatal tetanus. Prefilled, needleless, single shot injection devices could lead to higher immunization coverage in both routine and mass immunization by providing the means for more people to give injections while not demanding special cold chain or disposal facilities.

The trend in industrialised countries is for more self-injection. Without the constraint of rigorous storage conditions, vaccines may be given in institutions by less trained personnel.

3.4. Impact of disease control strategies

A variety of supplementary immunization strategies designed to control or eliminate disease are being integrated into routine immunization services in both developing and industrialised countries. Polio eradication, measles control and tetanus toxoid immunization of women have already been mentioned. When global polio eradication is achieved, there will be pressure from many quarters to embark on the eradication of other diseases, probably beginning with measles. These mass immunization initiatives target very large populations globally and they challenge the system in a number of ways which will provoke change.

3.4.1. Making enough vaccine - in time

Oral polio vaccine was a convenient, as well as an effective, choice for polio eradication because the volume of production could be expanded relatively quickly to meet the needs of national immunization days. However, freeze dried vaccines can only be manufactured at the rate permitted by freeze drying equipment in which long term investments have been made. As stock piling of this vaccine is usually only possible in the liquid bulk form, the rate of immunisation will be limited by the rate of world production of the finished freeze dried product.

Simpler and faster drying methods described during this meeting could permit higher rates of production and, possibly, a standard uni-dose presentation for jet injection.

3.4.2. Rapid, safe economic injection

Jet injectors have already proved to be the fastest method of mass immunization by injection. When they were entirely reusable they were the least costly method of injection in use. Concerns over safety will increase the disposable components on this type of injector and will therefore raise the cost in use. But the risk of accidental needlestick will have been eliminated and the parts to be disposed will not be sharp.

To meet the needs of mass immunization approximately four working injectors and one spare will be needed per health centre with a population catchment of 20,000. The cost of these injectors per shot, including their amortisation and their disposable parts, will be less than the cost of a single auto-destruct syringe, (including safety-sharps box).

3.5. Safety first...

3.5.1. "Zero risk" technology

Injection safety will become a higher and higher priority in both industrialised and developing countries. This will be reflected in the demand for 'zero risk' technology and for minimal tolerance for abuse. Markets will be obliged by popular demand to pay for safety. The cost and practicality of zero risk levels of safety will vary widely according to the injection technologies:

- reusable syringes and needles are unlikely to ever meet these standards because of the high levels of user-compliance which are required and because the probability of accidental exposure to needlestick, contaminated flushing water and inadequately sterilized needles is high
- standard disposable syringes are also unlikely to meet zero-risk standards because of the risk of reuse and because of the risk of needlestick
- auto-destruct syringes and pre-filled uni-dose (UNIJECT) injection devices are the most likely of the syringe technologies to meet zero risk standards, but only if they address the issue of accidental needlestick and if they can be designed to meet all injection needs, not just the immunization market.
- the single most powerful driver for the development of jet injection in industrialised countries is likely to be the elimination of the needle. If the jet injection device cannot be reused, cannot inflict accidental injury and does not generate sharps for disposal, it will meet the highest conceivable standards of injection safety.

3.5.2. Uni-dose vaccine presentation

The single dose presentation was adopted by industrialised countries for safety, economics and patterns of practice. Private sector practitioners in these countries, who usually see very few patients requiring immunization at one time, find the single dose presentation convenient. Even public sector immunization clinics in the United States choose 50% of their vaccines in single dose format, despite the additional volume of storage and shipping.

Developing countries need to eliminate wastage to combat the rising cost of vaccines. The most economic way to achieve this now is to keep opened vaccine vials until they are completely used. But if single dose presentations become economic in the future, the safety and convenience of single dose presentations will be welcomed for small immunization sessions which are becoming the norm in developing countries.

In Indonesia and China, for example, UNIJECT single dose injection devices with needles have been used successfully in field trials using Hepatitis B vaccine. These field trials have been so well received in Indonesia that they have been spread to whole provinces and a new trial will begin using tetanus toxoid.

The integration of the vaccine presentation with the injection device offers three critical benefits to immunization:

- the vaccine container also serves as the injection device, thus saving money

- the means of administering the vaccine is guaranteed to be available with the dose of vaccine. This is a very important factor in developing countries where scarcity of injection devices often compromises safety.
- the injection technology (the needle or the jet injection nozzle) is designed correctly for the type of injection to be given and for the vaccine in the device.

Integrated devices have one potential disadvantage which will must avoided by standardisation. The proprietary ‘pairing’ of device manufacturers and vaccine manufacturers stimulates initial stages of development. For example, in 1992 a large vaccine manufacturer initiated the successful development of a proprietary single dose jet injection system named the IMULE¹⁰. But this pairing, in the longer term, could interfere with competition and hinder the optimisation of quality. The vaccine container should be standardised so that both the vaccine manufacturers and the device manufacturers remain free to compete to the advantage of the customer.

Opportunities exist to implement single dose liquid jet injectors in the near future for annual flu-shots and for traveller’s immunization in the United States. The cost of available unidose vaccines in the US vary, today, between 5 and 35 \$US per dose, so the cost of the device is small in relation to total costs of injection. But in the developing country market, the costs of single dose presentation and disposable jet injectors would be prohibitively high now, even when compared to the higher costs of new vaccines (Hepatitis B at 0.85 \$US per dose).

3.5.3. Powder injection

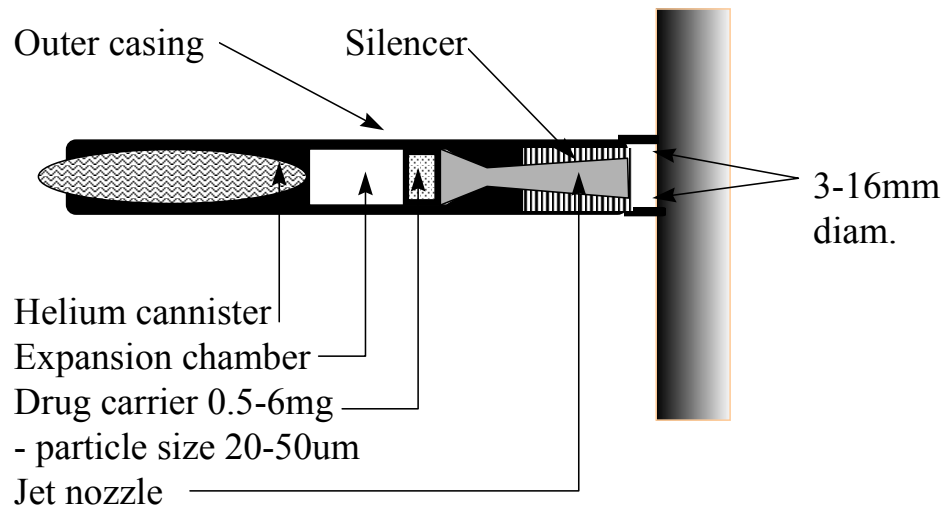
Powder injection technology, as we know it today, enables powders with particle sizes of 3 to 8 microns to be directly injected at speeds of about 800 metres per second into the intradermal and subcutaneous layers of children and adults. These layers have the advantage of highly efficient drainage and often show higher response more quickly than deep intramuscular injections. The technology of powder injection has important implications for the future of vaccine administration:

- it appears that powder can be injected without breaking the skin and is therefore no longer, technically, an invasive procedure.
- if the risk of cross infection is eliminated, reusable jet injectors could be safely used. This would minimise the disposal of waste and reduce the cost per injection significantly.
- powders are heat stable so that pre-filled injection devices may be stored at ambient temperature up to the time of administration
- powders may enable antigens to be combined more easily because dry particles can be designed to maintain their integrity with little or no chemical interaction
- the volume of powdered doses can be designed to be very small, thus enabling the packaging of the vaccine and the size of the device to be very small.

¹⁰ “Un progrès dans le domaine de l’injection sans aiguille: le système Imule”, M.Galy et al. S.T.P Pharma Pratiques 2 (4) pp 261-266 1992

- the distribution of the powder in the intradermal and subcutaneous layers is highly accurate and controllable. The surface area of the particles is very great, enabling a much faster rate of absorption than liquids.

Oxford Biosciences *Powderject*



Freeze dried vaccines are not ideal powders for jet injection. Their particle size is on the lower limit for jet injection and they are intensely hygroscopic, becoming unmanageable in the lowest relative humidities. Although there may be methods for transforming freeze dried powders to improve their characteristics, it seems more likely that an alternative drying method should be found.

Spray drying in the presence of trehalose is a promising solution because it is zero-reactive in tissues, and there are other methods. If future vaccines can be dried for powder injection and if powder injection proves to be a functional route of parenteral administration of vaccine, then this will be the safest method of injection for vaccines.

3.6. Concerns of industry

The strongest and clearest common concern of industry, regulators and the agencies is that global policies should be reached by a process of collaboration and that, in the case of future changes, this process should start as early as possible. Naturally this means that opinions and information are shared openly at a stage when decisions have not been made and directions have not been set.

3.6.1. Vaccine producers

Nearly two thirds of the vaccine now made for developing countries is made in the largest developing countries and the remainder is made in the west. Whether the proportion made in developing countries is to decline or to grow in the future depends on the speed with which new vaccine manufacturing technologies reach these countries. This, in turn, will strongly affect the rate of implementation of new and combination vaccines and it will affect the implementation of standardised containers for vaccines, whether or not they are integrated with the injection device technologies.

Today, the message from the International Federation of Pharmaceutical Manufacturers and already several of their members from industrialised countries is that neither the traditional glass vials used to present injectable vaccines nor the standard dose volume (0.5ml) should be changed for the following reasons:

- changing the presentation of existing vaccines requires most of the regulatory procedures which would be necessary to create a new vaccine
- a new presentation will require fundamental changes to filling and packing lines which will require heavy investment and subsequent rises in the cost of vaccine
- unless glass is to continue to be used, which is unlikely with integrated jet injection systems, the long term compatibility of plastic materials and their porous nature will present a major technical problem for producers
- integration of the vaccine presentation with the injection device, even if standardised, will require that different presentations will be needed for the syringe and needle and for the jet injector - and possibly for other routes of administration such as spray inhalation. This will further complicate the production process.

It is evident that to change the presentation of current or future vaccines is a large step, requiring thorough analysis of the anticipated costs and benefits to the major vaccine markets in both industrialised and developing countries. Therefore, if changes appear to be worthwhile, they are more likely to be feasible for new vaccines than for the traditional vaccines in use today.

3.6.2. The injection device manufacturers

The manufacture of syringes and needles is extremely well established in both industrialised and in developing countries. By contrast, the jet injection industry is very small and not yet very financially secure. The Association of Needle-Free Injector Manufacturers was formed only in February this year with a membership of 19 (See Annex 2).

These manufacturers include three principle groups:

- those who, for many years, have manufactured multi-dose, liquid, reusable jet injectors and who are now working to ensure that these can be made safe
- those who are developing or producing in small quantities, single-dose, liquid, disposable jet injectors with some kind of integral presentation of the drug/vaccine
- those who are developing powder jet injectors

The spokesman for the Association, while welcoming the new multi-agency Steering Group for the Development of Jet Injection, urged the Group to concentrate on the necessary market research which will provide the direction and confidence to the device manufacturers and their financial investors both for the short and the long term. The jet injector manufacturers point out that jet injection is not mentioned at all in the WHO/GPV internet home page, nor in the entire WHO web site at present.

At present there is virtually no dialogue between the vaccine industry and the jet injection device industry. In contrast, some device manufacturers report a growing dialogue with the pharmaceutical industry and, of course, there has been a long and fruitful collaboration between the insulin producers and the injection device manufacturers which can be expected to extend to jet injector manufacturers as this alternative to pen injectors develops.

A reported trend in the pharmaceutical industry appears to be towards the integrated presentation of other drugs in addition to insulin in pre-filled injection devices (usually with a needle incorporated). This is causing the 'proprietary pairing' which has already been mentioned and which, in the view of the Association, is not in the long term interests of the device industry, even though this investment would be welcome to jet injector manufacturers in the short term. 'Open architecture' standardisation of vaccine containers has already succeeded for the insulin industry and should be pursued for vaccines.

3.6.3. National regulators

Regulation agencies were not well represented at this meeting. However, during the Atlanta meeting in October 1996 it became clear that jet injectors in the United States, U.K, France and Italy had been 'grandfathered in' without national regulatory controls. The reason for this appeared to be the long history of use of jet injectors without recorded mishap.

The Food and Drug Administration of the United States informed the Atlanta meeting that they intend to review the status of jet injection devices with a view to develop such regulation in the near future. The EEC regulators present at the Meeting on Pen Injectors in London in February 1997 raised the problem that regulations are split widely between those affecting auto-injection devices (with needles) and those relating to pharmaceuticals. Integrated vaccine delivery systems will need regulation which spans both vaccine presentation and injection devices.

It is important that the process of setting new regulations takes place in collaboration with both industries and with WHO and national public health agencies, such as CDC.

4. IMMEDIATE PRIORITIES

4.1. Market needs

The greatest market needs for injections are:

- to improve the safety of injections by syringe and needle in developing countries
- to make multi-dose jet injectors available for mass immunization which meet ‘zero-risk’ standards of safety for all markets
- to make available single dose jet injection for industrialised countries

The second and third of these issues are the priority concerns of this Steering Group.

4.2. Make available multi-dose jet injectors

Table 1 shows a representative range of devices using multi-dose vaccine vials.

Table 1: Types of jet injectors using multi-dose vaccine vials

Injector model	Power source	Type	Consideration
AM-O-JET	Hydraulic, foot pedal	Hydraulic propelled steel spring	<ul style="list-style-type: none">• Reusable nozzle• Reliability of footpump
MED-E-JET	CO2 cylinder	Gas propelled steel spring	<ul style="list-style-type: none">• Availability of gas• Reusable nozzle
SICIM	Hand crank	Screw propelled steel spring	<ul style="list-style-type: none">• Auto-destruct nozzle, supply and disposal
DERMOJET	Hand cock	Lever propelled steel spring	<ul style="list-style-type: none">• ID only
MEDIVAX	CO2 cylinder or footpump	Gas spring with piston	<ul style="list-style-type: none">• Auto-destruct nozzle and fluid pathway

The AM-O-JET injector, which is a development of the PED-O-JET injector, and the MEDEJET injector have been the most widely used for mass immunization in developing countries for more than 40 years. The DERMOJET is a small hand-held injector for intra-dermal injection. All these types of injector propel the vaccine dose through a reusable nozzle which is in contact with the skin of multiple clients. The SICIM injector, a development of an insulin injector, has a similar mechanism but ejects the nozzle automatically after each dose. All these models of injector use steel springs to provide the necessary driving force. The steel springs are cocked manually, by hydraulics and footpedals or with CO₂ gas.

The MEDIVAX injector, which was developed to an earlier version of the performance specification which appears as Annex 3 to this report, uses compressed air as a spring to drive a piston down a disposable vaccine reservoir and single use nozzle. Thus, the entire fluid pathway is discarded after a single use. The prototype cost of this assembly is 0.90 \$US but it is expected to fall to 6 US cents in production. The steel spring injectors are

damaged by dry-firing (without vaccine) whereas the MEDIVAX is protected from dry-firing.

Jet injectors, such as the MEDIVAX and the SICIM are 'hybrid' in comparison to their predecessors. They meet the needs of the developing country market for mass immunization. They also meet the needs of industrialised countries for small sessions of 10 to 20 children and the requirements of other institutional vaccination, such as the military.

4.2.1. Safety concerns

The multiple use nozzle jet injector most widely used (PED-O-JET) has never been implicated in transmission of blood-borne diseases. However, one report of an outbreak of hepatitis B caused by non-compliant use of another type of multiple use nozzle jet injector (MEDEJET) in a weight loss clinic¹¹, and laboratory studies in which blood contamination of jet injectors has been simulated have caused concern that use of multiple use nozzle jet injectors may pose a risk of blood-borne disease transmission to vaccine recipients. In addition, studies in Brazil with PED-O-JET have shown that under field conditions the ejected vaccine was positive for occult blood by urine dipstick testing in 0.2% to 6.6% (1% average in 2880 injections) of inoculations.¹² At the time of this study, it was believed that the mode of contamination was likely to be the contact surface of the nozzle.

4.2.2. Bovine immuno-assay testing

The Public Health Laboratory Service, UK, reported preliminary results from tests carried out during 1997 on the MEDEJET injector with the same nozzle as that implicated in the California outbreak. In this series of tests 200 injections were conducted on calves, each injection being followed by a series of shots into test tubes. Both the ejectate and the swabbed deposits on the injector head were collected separately. All samples were analysed using a bovine albumin immuno-assay developed for the study.

The results, which are to be published, showed systematic contamination of the ejectate, persisting after the first flushing shot. Moreover, the levels of contamination were consistently higher than those which could be explained by the contamination of the nozzle by contact with the calf skin during the injection. A hypothesis was therefore advanced, that the path of contamination may have been reflux within the jet stream. This could possibly have occurred at the end of the shot when the liquid pressure at the nozzle of the injector dies to a level lower than that of the liquid column within the skin and subcutaneous tissue of the animal.

¹¹ Canter.J et al. "An Outbreak of Hepatitis B Associated with Jet Injections in a Weight Reduction Clinic", Archives of Internal Medicine. 150:1923-1927, September 1990.

¹² Brito, Glacus et Al. "Multi-dose jet injectors and safety aspects in Brazil" Jet Injectors for Immunization - Meeting Atlanta October 2-3 1996

The implication of these results is that, for jet injection to be safe, the entire fluid path must be changed between injections. However, it was recognised during the meeting that:

- there is no relation yet established between jet injections into calves and those into humans,
- the test has only been conducted on a single injector model, and one which has already been implicated in disease transmission,
- the reliability of the ELISA assay, while being sufficient to draw the above conclusions with confidence, requires improvement even to consistently reach 10^{-6} per litre sensitivity. This is still two orders of magnitude too low to reflect risks of hepatitis B infection
- interim reports have not been released to industry during the laboratory work because of the unexpected data which has been emerging. There is a need now for the device industry to conduct their own testing with the same rigour to verify or refute these results.

4.2.3. Gross contamination testing in-vitro

Laboratory test results were presented by the Programme for Appropriate Technology in Health (PATH) USA based on the gross contamination of the nozzle of the jet injector . The tests are designed to detect contamination in three areas: 1. On the “skin” surface (the surface of a Parafilm cover of the sample cup), 2. In down-stream inoculations between patients, and 3. On the skin-contact surfaces of the jet injectors tested. These tests detected contaminants to a sensitivity level of 10^{-6} ml.

The presence of blood on and within the injector nozzle was examined using fluorescent photography and the ejectate was tested with Bayer Hemastix. Although these tests were not as sensitive as the PHLS tests, they showed systematic contamination of both the ejectate and the internal fluid pathway.

4.2.4. Field trial plans

To establish some relation between the contamination phenomena observed in laboratory safety testing and those which would be expected in humans, a protocol for field trials in Brazil were presented to the Steering Group. In this trial, 1000 military recruits will be exposed to 2 shots each of vaccine from sterile AM-O-JET jet injectors and, if they have been cleared by laboratory tests at the PHLS, one shot of sterile saline each from MEDIVAX and SICIM jet injectors. Each injector will be swabbed and fired two more times into separate test tubes to collect the ejectate. The swabs will be collected in a third test tube and the tubes, including a control before the injection is made, will be coded and sent to the PHLS laboratory.

The PHLS laboratory will then perform tests blind using a human albumin immuno-assay and, in parallel, by the phenolphthalein test for the heme protein in haemoglobin. The results will be decoded and compared to the in vivo and in vitro test results.

If these tests yield good results for the MEDIVAX injector, plans exist to run a short limited trial of production prototype injectors in Indonesia in the second half of 1997 and a larger field trial on final production injectors in Philippines early in 1998.

4.3. Make available single dose jet injectors

Compared to the multi-dose injectors discussed in the previous section, single dose jet injectors are a more recent concept using direct, high pressure helium gas as a propellant. The expansion of helium is sufficiently fast and powerful to drive the vaccine in liquid or in powder form through the appropriate jet nozzle without the necessity of a steel spring or a reusable, low air pressure piston.

The significance of this development is that the engineering of the injector becomes sufficiently simple to permit the disposal either of the entire injector, or of the helium capsule and the vaccine container/nozzle, leaving the sleeve in which these are housed to be reused. The cost of manufacture of one such device for liquid presented at the meeting was 0.22 \$US.

Smaller standard doses (0.1ml) would allow the injector to be reduced in size: prototype liquid injectors were shown at the meeting which were the size of a clinical thermometer.

A serious constraint with both powder and liquid injectors of this type is that, until a standard vaccine container is agreed with the vaccine manufacturers, vaccine must be loaded into the single dose disposable containers and stored until they are used. This limits such trials, at this point in time, either to human trials where the vaccine is loaded 'on-site' which is scarcely practicable, or to immunogenicity studies in animals.

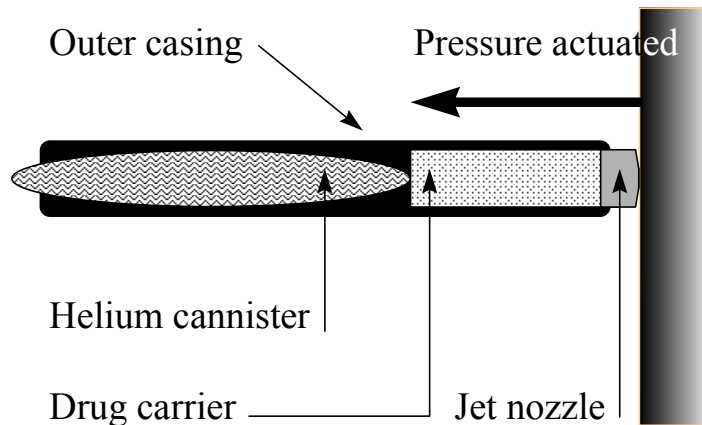
Table 2: Types of single dose jet injectors for pre-filled vaccine containers

Injector model	Power source	Type	Consideration
INTRAJECT	Helium capsule	Gas spring without piston	<ul style="list-style-type: none">• Single use liquid injector
POWDER-JECT	Helium capsule	Gas spring - rocket science	<ul style="list-style-type: none">• Disposable drug vial and energy capsule and reusable injector

4.3.1. Liquid

At least one manufacturer of this type of injector already exists (Weston Medical, UK). Weston have produced a number of prototypes adapted to different purposes and they have a model, INTRAJECT, made for liquid injection of DNA. Weston have demonstrated, with a prototype, that it would be possible to mount up to 6 single dose injectors in a pistol grip which could deliver multiple antigens simultaneously to adjacent vaccination sites.

Liquid jet injection (Weston UK)



A search will be made for other manufacturers and discussions will begin with this manufacturer and the vaccine manufacturers to plan for early tests and trials which would lead towards the standardisation of appropriate vaccine containers for long term storage.

4.3.2. Powder

Oxford Biosciences (UK) has global patents covering the jet injection of powdered drug. Three prototype products are in development at the company:

- Powderject: single shot disposable with drug cartridge (\$US 1.70), reusable body (\$US 17.00) and helium cartridge (\$US 0.50)
- Oralject: for injection into the mouth
- Accell: For gene delivery

The immediate priority is to study the immunogenicity of a freeze dried vaccine when injected directly into a suitable animal model. WHO/GPV/VRD plan to collaborate with RIVM (Netherlands), Oxford Biosciences and vaccine manufacturers to load the drug cartridge with freeze dried vaccine and to study in puppies:

- the immunogenicity of 1/5, 2/5, 3/5, 4/5, and 1 standard infant dose of measles vaccine when the puppy is challenged with distemper virus
- the dispersion of the vaccine in the dermal and subcutaneous layers of children
- the effect of processing of vaccine particle sizes on immunogenicity and dispersion.
- the container technology required for the long term storage of powdered vaccines

4.4. Timetable for action

An outline plan appears in the Gant chart below:

Objective/Activity:		1997		1998		1999
STEERING GROUP MEETINGS		1st	2nd	1st	2nd	1st
1.0	Evaluate jet injection of liquid vaccine	▲	▲	▲	▲	▲
1.1	Assess safety of jet injectors using existing multi-dose vials <ul style="list-style-type: none"> • PHLS bovine test :Med-E-Jet • PHLS bovine test :MEDIVAX, AM-O-JET, SICIM • field safety trial: Brazil • CRL Endurance testing: SICIM, MEDIVAX • preliminary field trial: Indonesia • field introduction trials: Philippines, MEDIVAX • industrial production/introduction • post marketing impact studies 					
1.2	Assess single dose jet injectors (liquid vaccine) for vaccine administration <ul style="list-style-type: none"> • agree performance specification • market search/solicitation • mechanical testing in lab. • packing & clinical testing with vaccine • field trials 					
2.0.	Investigate the jet injection of powder vaccine					
2.1	<ul style="list-style-type: none"> • (GPV/VRD)Investigate the immunogenicity of measles vaccine powder injected into animal model: <ul style="list-style-type: none"> • using 1/5 to full dose 					
2.2	<ul style="list-style-type: none"> • (GPV/VRD)Investigate an alternative vaccine model for: <ul style="list-style-type: none"> • spray drying feasibility • immugenicity & safety 					

4.5. Evaluating future scenarios

The Group agreed that a rigorous analysis should be made with the help of the vaccine and the injection device industries to evaluate a number of probable future scenarios of market demand. In the meantime, the discussions generated the following directions in thought about the more compelling aspects of the future.

4.5.1. Measles eradication with which vaccine?

If injection safety can be assured by the development of safe, multi-dose jet injectors then measles can be eradicated with the current measles vaccine, in spite of the inconvenience of reconstitution. The problem will be to assure the availability of enough vaccine and enough money to buy the vaccine.

Direct injection of a powdered measles vaccine or direct injection of a stable liquid measles vaccine, without reconstitution, by jet injector would appear to offer significant advantages for mass immunization. However, if the process of eradication is to start by the end of the century it is probably not possible to modify the presentation of the current measles vaccine because of the process of regulatory approval. A modified measles vaccine would require most of the investment needed for a completely new vaccine.

4.5.2. Can we reduce the standard dose?

Reducing the volume of the standard dose, particularly for liquid vaccines, will bring benefits including lower pain thresholds, more compact single dose formats and lower cost jet injectors. However these statements need to be supported by rigorous analysis and the immunogenicity of smaller doses needs to be examined.

4.5.3. Single dose vaccine worthwhile for Developing Countries?

The future scenario of higher vaccine prices, lower tolerance for wastage and 'zero-risk' standards of safety need to be examined to see, if all immunization delivery costs are taken into account and savings such as those on the vaccine cold chain, could single dose vaccine be worthwhile in developing countries in the future.

4.5.4. Can the cold chain go: how and when?

The costs, and the problems, of the refrigerated chain for vaccines is the greatest at the periphery. The costs of replacement of the cold chain are steeply increasing to keep pace with the programme of eliminating chloro-fluoro-carbons (CFCs), including the change of all refrigeration equipment design, by the year 2005 in developing countries. This programme is likely to be accelerated to 2002 or 2003.

Heat stable vaccines will result in immediate benefits in flexibility of field operations and in potency at the point of use. But savings from the elimination of the cold chain (about 3 \$US per fully immunized child per annum) could not be realized until all vaccines are stable. Forecasts of the impact of cold chain savings need to be assessed and used in building scenarios in which all system costs are considered.

4.6. Investigation into new standard presentations of vaccine

A dialogue will begin between members of the Steering Group, the vaccine industry and the device industry to plan the most appropriate strategy to investigate the feasibility, effectiveness and cost of:

- reducing the standard vaccine dose (childhood) to 0.1ml for jet injection

- alternative methods of drying existing and future vaccines
- alternative methods of suspending stable dried vaccines in non-aqueous liquid solutions

5. CONCLUSIONS AND RECOMMENDATIONS

5.1. *Jet injection in the short term : Multi-dose, reusable jet injectors*

5.1.1. Safety testing in animal models

The Group noted with concern evidence presented by the Public Health Laboratory Service, UK that systematic contamination of the fluid path and vaccine reservoir is observed in animal tests of the MED-E-JET jet injector. The mode of contamination is not explained by contamination of the nozzle or surface in contact with the skin. A hypothesis has therefore been proposed that contamination of the fluid path occurs along the jet-stream at the end of the shot when pressures in the liquid column at the site of the injection begin to exceed the pressures at the injector head.

5.1.2. Safety testing in-vitro

Similar conclusions can be reached from the results of parallel tests in-vitro on the PED-O-JET (now AM-O-JET) at the Programme for Appropriate Technology in Health (PATH - USA). These tests confirmed a correlation between the extent of contamination and the level of back-pressure in simulated skin models. However, neither the animal nor the in-vitro tests have been confirmed in humans to date and the testing has not included all injectors now available for immunization.

5.1.3. Recommended actions

- Perform parallel human tests in the field, human albumin assay and laboratory tests on the bovine model using the AM-O-JET to determine whether this mode of contamination occurs systematically in both animals and humans.
- Complete laboratory tests now in progress on the bovine model using the SICIM injector and conduct these tests also for the MEDIVAX injector.
- Depending on the result of this test, conduct limited human field trials using production prototypes of the MEDIVAX jet injector and to plan large scale trials for the start of 1998
- Conduct gross contamination laboratory tests in-vitro on the SICIM injector.
- Promote the development alternative models of safe, jet injectors for multi-dose vaccine presentations by:
 - finalising and to distributing to the industry the current WHO draft performance specification
 - to prepare and distribute to the industry market estimates for this product.

5.2. Jet injection in the long term : Disposable jet injectors for single dose vaccine presentation

5.2.1. Benefits

The Group recognised that there appear to be significant benefits inherent in single dose, standardised presentation of liquid or powder vaccine for use in jet injectors including safety, avoidance of vaccine wastage and ease of use which may increase immunization coverage in developing countries and would improve safety in all countries.

Additional benefits could result from the reduction of the volume of the standard liquid vaccine dose five-fold including improved acceptability for multiple, simultaneous injections which is an immediate priority in industrialised countries and a future priority in developing countries. Reducing the liquid dose volume or adopting powder injection technology should enable simpler, lower cost jet injectors to be developed.

5.2.2. Constraints

On the other hand, a change from the standard presentation in multi-dose vials would present vaccine manufacturers with a number of problems including the renewal of filling lines, lower rates of vaccine production, compatibility testing and regulatory hurdles. In addition, the device industry would also have to invest in the development of new injectors specifically tailored for this purpose. Finally, vaccine presented in this way may need to be stable enough to be removed from the cold chain because of the increased storage volume required.

5.2.3. Recommended actions

Therefore, to better evaluate the costs and the benefits of this injection technology to immunization programmes in developing countries, the Group recommends that the following activities be pursued:

- to evaluate, in the field conditions of both developing and industrialised countries, one or more existing single dose, disposable injectors filled experimentally with a standard liquid vaccine. The injectors will be used to give subcutaneous or intramuscular injections in children under one year.
- to develop scenarios based on assumptions of the potential market, price points, and products to assess the probable cost and impact on production of using standard single dose container for jet injection and validate these with the manufacturer.
- to evaluate, with industry, the effectiveness, feasibility and cost impact of :
 - reducing the volume of the standard vaccine dose
 - alternative methods of drying vaccine
 - direct jet injection of powdered vaccine
 - suspending stable powder vaccines in non-aqueous liquids.

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ANNEX 3

Draft Performance Specification for Multi-dose Jet Injectors

MULTI-DOSE JET INJECTOR FOR IMMUNIZATION

Draft requirements¹³ - 16-01-97

Jet injectors are needed for parenteral vaccine administration primarily in mass immunization campaigns but potentially in all immunizations. They must demonstrate adequate safety, reliability and performance at a cost in use which competes with the auto-destruct syringe, including costs of safe disposal of contaminated waste (Approximately 10 cents US per injection).

Vaccine compatibility	<ul style="list-style-type: none">• Materials of fluid path compatible with current vaccines
Volume of dose	<ul style="list-style-type: none">• Reservoir device accepts glass vial sizes up to 50ml• 0.5ml for SC injections OR• 0.05ml and 0.1ml to ID injections
Type of injection	<ul style="list-style-type: none">• Subcutaneous injection in infants under 1 year or• Intradermal injection of new-borns
Rate of injection	<ul style="list-style-type: none">• Minimum rate 4 injections per minute
Safety	<ul style="list-style-type: none">• The risk of cross infection (downstream and contact surface transmission of blood) inherent in correct operation of the device must be shown to be zero when tested according to the current WHO standard procedures
Bleeding rate	<ul style="list-style-type: none">• Less than 5% rate of visible bleeding within 3 seconds of the injection in 1000 injections of vaccine or sterile saline
Cleaning	<ul style="list-style-type: none">• The exposed external surfaces of all parts must be easily cleaned
Disposability	<ul style="list-style-type: none">• At least the nozzle, any surfaces in contact with the skin and components containing fluid pathways must be disposable.• The disposable parts and assemblies shall not be able to be reused to give a second injection• The disposable parts or assemblies should not be sharp enough to cause injury• The vaccine reservoir should be isolated from any component or pathway which participates in the process of the injection stroke• Other reusable components should either be unable to be a source for cross contamination or should be

¹³ Based on "Low Workload Jet Injectors For Vaccine Delivery" Meeting on Jet Injectors for Immunization 2-4 October 1996

Comfort	steam sterilized (+126C, 20 minutes) daily without impairing the performance of the injector
Energy source	<ul style="list-style-type: none"> • Standard to be defined • Compressed gas/air or human mechanical/hydraulic or electrical (at least 50 injections capacity per electrical or gas storage device)
Physical size/weight	<ul style="list-style-type: none"> • Portable, able to be held in one hand by female operators easily during the injection
Durability	<ul style="list-style-type: none"> • Injectors should not require trained technician maintenance in normal use before 25,000 shots with sterile saline. • “Dry” firing should either be impossible or should not affect the durability up to 200 dry firings distributed randomly within the 25,000 shots with liquid • Should not be damaged by standard drop test