technical review
of vaccine
vial monitor
implementation

27 March 2002, Geneva
World Health Organization
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VVM FOR ALL

Technical Review of Vaccine Vial Monitor Implementation

World Health Organization, 27 March 2002, Geneva

Chair: Dr. Mercy Essel Ahun, Immunization Programme Manager, Ghana
Rapporteur: Ms. Debra Kristensen, Technical Officer, PATH, Seattle

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Executive Summary

A one-day technical session on Vaccine Vial Monitor (VVM) implementation, part of the World Health Organization/United Nations Children’s Fund (WHO/UNICEF) action plan on VVMs, was held on 27 March 2002 at WHO Headquarters in Geneva. The meeting served as a forum to review progress to date and discuss remaining technical and logistical concerns regarding VVM implementation. A total of 50 representatives from vaccine manufacturers, time-temperature indicator technology companies, and other partners as well as staff of WHO and UNICEF participated in the meeting.

VVMs are now available for vaccines other than OPV and have been included among the minimum requirements for vaccines purchased by UNICEF in all vaccine tender documents since 2000. Despite this, only five of 23 UN pre-qualified vaccine manufacturers have complied with the attachment of VVMs on BCG, yellow fever, measles, MR, MMR, hepatitis B and TT (Uniject) for UNICEF-procured vaccines. Other manufacturers have requested additional time to make required adaptations.

The participants agreed on the invaluable role of VVMs in improving the quality of immunization efforts throughout the world. With regard to regulatory concerns, it was agreed that it is the responsibility of vaccine manufacturers to contact national regulatory authorities, with assistance from WHO and LifeLines as required to resolve issues. However, WHO agreed to continue working to informally contacting regulatory authorities. WHO also agreed to address the issue of whether a regulatory review is required for countries receiving vaccines with VVMs. PAHO agreed to explore the positions of regulatory authorities in the Americas with regard to acceptance of VVMs on vaccines.

It was noted that liability issues exist with or without VVMs, and VVMs do not add additional liability. On the contrary, they reduce the liability of vaccine manufacturers. However, it was agreed that individual manufacturers might want to seek legal counsel and act accordingly.

Participants agreed that validation and conformity studies should follow WHO standard test procedures (E6/PROC/5 dated 25 March 2002) and product specifications (E6/IN5 dated 25 March 2002). In the case of some manufacturers needing additional testing to meet internal or national regulatory authority requirements, LifeLines offered to work with them to study additional testing that might be required.

With regard to logistical issues, LifeLines agreed to continue working closely with vaccine manufacturers to identify the best solutions for label applications.

WHO agreed to take the lead in collecting feedback from the field on vaccine management to document the impact of the VVMs, and to share the data with interested parties, including vaccine manufacturers.

The meeting was considered a milestone as it resulted in a valuable exchange of information, clarification of issues, and assignment of responsibilities for all parties. The promise of inclusion of VVMs on all vaccines for the public sector has not been fulfilled to date. It is expected that following the meeting, VVM implementation on all vaccines will be accelerated, providing an important tool to countries for vaccine management.
VVM is the only tool among all time temperature indicators that is available at any time in the process of distribution and at the time a vaccine is administered indicating whether the vaccine has been exposed to a combination of excessive temperature over time and whether it is likely to have been damaged. It clearly indicates to health workers whether a vaccine can be used.
Technical review of Vaccine Vial Monitor implementation

Background

Vaccine Vial Monitors were first included on vials of OPV in 1996 and are being widely and effectively used both in routine programmes and supplementary immunization activities such as national immunization days (NIDs). Because of their proven utility in vaccine management, WHO and UNICEF issued a policy statement in 1999, “Quality of the cold chain: WHO/UNICEF policy statement on the use of vaccine vial monitors in immunization services (WHO/V&B/99.18)”, which states the value of VVMs and recommends that agencies purchasing vaccines request manufacturers to supply all vaccines with VVMs that meet WHO specifications. VVMs on vaccines other than OPV started to become available in 2000. During 2001, many countries began to receive BCG, yellow fever, measles and/or MMR vaccines with VVMs.

The placement of VVMs on vaccine vials either through integration with the product label or as a separate label represents a change in labeling practices by the vaccine manufacturers. In order to facilitate this process, WHO in coordination with UNICEF has been working with the vaccine manufacturers for some time.

In August of 1999, at the 5th Round Table on Vaccine Supply in Copenhagen, UNICEF announced that, according to the WHO-UNICEF joint policy statement on the use of VVMs in immunization services, future vaccine solicitation requests would require VVMs on all vaccines beginning in the year 2000, with full implementation to be achieved no later than January 1, 2001. All solicitations since that time have specified that vaccine vials include VVMs. Since then, several manufacturers have offered to provide the requested vaccines with VVMs, but most have requested additional time to make the required adaptations.

In 2001, UNICEF Supply Division requested vaccine manufacturers to bring up issues impeding VVM implementation. The technical, logistics and commercial concerns were gathered and discussed with UNICEF and WHO. Based on the feedback from the vaccine manufacturers, WHO and UNICEF developed an action plan to expedite VVM implementation. WHO responded to technical and logistics concerns with a letter dated 23 August 2001. Visits have been organized to several vaccine manufacturers. Finally, this one-day technical review meeting on VVM implementation was held on 27 March 2002 at WHO Headquarters in Geneva.
Gains in polio eradication over the last 10 years would hardly have been feasible without VVMs, especially in areas such as Sudan and Somalia.
Objectives

The purpose of the meeting was to provide an open forum for vaccine producers in which all previous technical questions and responses about VVM implementation were conveyed and discussed.

Objectives of the meeting were to:
1. Highlight the value of VVMs based on experience to date,
2. Summarize the constraints identified by the manufacturers,
3. Review the response to these constraints, and
4. Agree on action points for full implementation of VVMs on all vaccines.

The meeting represented an opportunity for vaccine manufacturers to express any remaining technical questions. Questions were accumulated during the beginning of the meeting, grouped by topic, and responded to at the end of the meeting. A summary of the major points raised during the meeting and a list of action points agreed upon by the participants follows.

Opening

Dr. Heymann, Executive Director, Communicable Diseases and Surveillance Cluster, WHO, welcomed all on behalf of the Director General. He acknowledged that sensitivities and issues exist with regard to VVM implementation, but confirmed that UNICEF and WHO strongly consider VVMs to be a priority and hope that the meeting would result in action that paves the best way forward.

Dr. Ahun, Immunization Programme Manager, Ghana acknowledged the contributions of vaccine producers to immunization efforts and expressed her hope for useful contributions on how to move forward during the meeting.
VVMs have also become an invaluable tool to increase coverage through increased access in hard-to-reach communities and in areas with very weak and no cold chain infrastructure.
Dr. Kartoglu reviewed the history of VVM implementation. Milestones can be summarized as follows:

1996  VVMs were first included on OPV vials and have been widely used since then.
1999  WHO/UNICEF issued a joint policy statement on the use of VVMs in immunization programmes.
1999  After an extensive review, WHO issued VVM technical specifications for all vaccines.
2000  VVMs were included among the minimum requirements for vaccine purchased by UNICEF in tenders and in the RFP issued by UNICEF on behalf of the GAVI Vaccine Fund.

VVMs became available for all vaccines in 1999. Chiron Italy, Japan BCG, and Institut Pasteur Dakar were the first to move forward with VVM implementation on measles, MR, MMR, BCG and yellow fever vaccines. In 2001, with pre-qualification of TT Uniject, Bio Farma become the fourth vaccine manufacturer complying with VVM implementation for vaccines other than OPV. LG Chemical Inv. Ltd., joined this group in late 2001 with VVM implementation on hepatitis B vaccine.

Table 1 (below) provides a list of countries that have received vaccines with VVMs:

Table 1. Where are they? VVM implementation by vaccine type, 27 March 2002

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPV</td>
<td>All countries receiving OPV from UNICEF and/or using UNICEF procurement services for OPV purchase</td>
</tr>
<tr>
<td>BCG</td>
<td>Syria, North Korea, Nepal, Philippines, East Timor, Cambodia, Pakistan, Myanmar, Bangladesh, Jordan</td>
</tr>
<tr>
<td>YF</td>
<td>Burkina Faso, Gambia, Chad, Angola, Mali, CAR, Benin, Kenya, Pakistan</td>
</tr>
<tr>
<td>Measles</td>
<td>Ghana, Vietnam, Cuba, India, Pakistan, Morocco, Burundi, Kenya, Tanzania, Uganda, Rwanda, Zaire, Nigeria, Congo, Sierra Leone, Croatia, Macedonia, Albania, Lebanon, Jordan, Syria</td>
</tr>
<tr>
<td>MMR</td>
<td>Colombia, Cuba, Syria, Yugoslavia</td>
</tr>
<tr>
<td>HepB</td>
<td>Albania, Azerbaijan, Bangladesh, Benin, Cambodia, Cape Verde, Fiji, Gabon, Kyrgyzstan, Lebanon, Moldova, Mongolia, Morocco, Pakistan, Russia, Spain, Turkmenistan, Uzbekistan, Yemen, Yugoslavia, Zambia</td>
</tr>
<tr>
<td>TT</td>
<td>Indonesia, Uganda, Burkina Faso</td>
</tr>
</tbody>
</table>

Source: Compiled data from WHO, Vaccine manufacturers, LifeLines
Dr. Kartoglu also showed growth in VVM availability since 2000 – largely due to polio NIDs and addition of VVMs on new vaccines.

*Figure 1. The growing trend in VVM global use, LifeLines, 1996-2002*

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**Comments and questions:**

**Question:** Is there any feedback on the VVM training status for other vaccines?

**Answer:** VVM training guidelines have been revised and updated to cover all types of VVMs. The draft was shared with a group of countries and WHO is receiving positive feedback on the new revisions. The most recent example is the Vietnam measles campaign where the revised training guidelines were used. WHO hopes to finalize the training guidelines in a couple of months for final publication.
Dr. Ahun gave a presentation on the programme perspective of VVMs. VVMs are needed to make an informed choice about whether or not to use a vial of vaccine, to address access problems, shortages of kerosene gas and electric supply, and aging cold chain equipment. The VVM is the only tool that is available at all times (during distribution and storage as well as when the vaccine is administered) indicating whether the vaccine has been exposed to a combination of excessive heat over time and whether it is likely to have been damaged. Temperature data loggers are used mostly to monitor international transport. Cold Chain Monitor cards are used to monitor transport between levels, and STOP!Watch is used to monitor refrigerator temperatures (See re 2).

Many immunization programmes recommend discarding vaccines if storage temperatures exceed 10°C without VVMs. VVMs can provide a tool for informed choice. VVMs have also become an invaluable tool to increase coverage through increased access in hard-to-reach communities and in areas with very weak and no cold chain infrastructure. Ghana has had VVMs on OPV since 1996, and some VVMs on
measles in 2000 (supplied by Chiron). VVMs help prevent delivery of heat-damaged vaccine, reduce vaccine wastage, indicate cold chain problems, serve as a tool to manage vaccine stocks, and facilitate immunization outreach. Volunteers have used them effectively to increase coverage in hard-to-access areas during polio National Immunization Days (NIDs). VVMs have engendered confidence in the immunization program. A Vaccine Management Assessment was conducted in Ghana in May 2001. The VVM portion of the assessment showed that all levels were using VVMs effectively to manage stock and were properly discarding vaccine with VVMs at Stage 3 and Stage 4. The field has a need for VVMs to help monitor vaccines effectively and to deliver vaccine not deactivated by heat. Today, the best contribution vaccine manufacturers can make would be to provide VVMs on all vaccines to make a difference in the life of a child.

Comments and questions:

Comment: Gains in polio eradication over the last 10 years would hardly have been feasible without VVMs, especially in areas such as Sudan and Somalia. It is a tool that has relevance at all levels. Even in large countries where we thought the cold chain functioned properly, it has allowed us to detect cold chain problems.

Question: On the issue of training - when the polio VVM was introduced, health workers at first reacted as if that they didn’t believe the VVM was working. But now this belief is no longer a problem. When you introduced the measles VVM, have you faced any such concerns or other problems?

Answer: Yes, as in other countries, Ghana had a few problems in the beginning with OPV VVMs, because people had previously believed that the vaccine couldn’t be out of the refrigerator for even a few minutes. VVMs helped to extend use of the vaccine. However, it has taken some time for health workers to become comfortable with the tool to make an informed choice. For measles VVMs, we have not had any field difficulties or concerns since people had gained comfort with polio VVMs.

Comment: Vietnam just had its first experience with measles VVMs in the most recent campaign which is currently still running. Vietnam had not used VVMs before (locally produced OPV was used for polio NIDs). Acceptance during the training and early days of the campaign was very good. The results are very encouraging. VVMs, for a very small cost, really help indicate to health workers whether the vaccine can be used. There is also another advantage of VVM placement on the cap of the freeze-dried vaccine: it forces the health care worker to look at it during reconstitution. In general, the Western Pacific region is extremely excited about having VVMs on vaccines.

Comment: WHO is conducting a VVM impact study on the use and distribution of measles vaccine in a campaign setting in Vietnam. The results will be shared with all parties when available. Examples of OPV VVM impact studies were included in the meeting folder.

Question: Has introduction of VVMs resulted in people not paying attention to the cold chain?

Answer: No, this hasn’t been a problem. People are still focused on using ice packs and properly handling the vaccine.
Comment: VVMs have helped countries to be more cautious about their cold chain.

Comment: Because the decision-making process with VVMs is in the hands of the health workers, the VVM has led to increased awareness of the cold chain.

Conclusion:

There is consensus that VVMs play an extremely valuable role in improving the quality of immunization efforts throughout the world.
How to read and interpret VVM messages were placed on all vaccine carriers during National Immunization Days in Africa.
Questions and concerns raised by manufacturers
presented by Dr. Ümit Kartoglu, WHO/HQ

In 2001, vaccine manufacturers raised some questions and concerns about issues impeding VVM implementation. UNICEF Supply Division facilitated further feedback on these issues through a specific letter on the general terms and conditions governing VVM procurement. WHO responded to all these questions on 28 August 2001. In addition to regular contact with vaccine manufacturers, WHO, in coordination with UNICEF, began visiting vaccine manufacturers on a one-on-one basis to discuss VVM implementation issues in detail. WHO compiled a list of all questions and prepared a Question & Answer (Q&A) document which was sent to all parties invited to this meeting and included in the meeting file. The questions were categorized as follows:

Validation issues
1. The shelf life of the VVM is less than the shelf life of the vaccine.
2. Will WHO conduct correlation studies for VVMs and vaccine potency for all vaccines?
3. Can the VVM consistently reflect the true stability of each vaccine?
4. What data exist to show how the VVM is validated?
5. Is there some typical specification for VVM adhesion?
6. Chemical temperature indicators produce a high percentage of false readings...

Logistics issues
1. Concerns about introducing a different labeling system for a portion of their production.
2. How to maintain the logistics of import and inventory control?
4. Additional capital expenditures to implement VVMs.
5. Does the current GMP requirement prohibit pre-printed labels or require an on-line printer with a blank roll?

Regulatory issues
1. Does VVM attachment to the vaccine vial need to be approved by the national regulatory authority?
2. Who is legally and financially responsible when a vial or shipment is rejected because the status of the VVM(s) indicates excessive heat exposure?
3. Does the manufacturer’s obligation cease at the time that the shipment is accepted in country?

Programme issues
1. What is the benefit of having a VVM on a vaccine that is very heat stable, such as hepatitis B?
2. Is the VVM color change clear, and does it convey the information to the field worker in a form that is easy to understand?
Commercial issues
1. LifeLines is the sole supplier of VVMs, there is no other competitor.
2. Why doesn’t the LifeLines warranty mirror the minimum shelf life required of the vaccine suppliers (18 months from the date of shipment from the vaccine supplier)?
3. Why does LifeLines have a +/-10% tolerance on the quantity of VVMs delivered?
4. Why does a minimum VVM order quantity have to be set?

Dr. Kartoglu explained that the meeting would not address the commercial issues, but encouraged vaccine manufacturers to contact LifeLines since many of the commercial concerns have been addressed.

Dr. Kartoglu asked all vaccine manufacturers to review the list of questions and raise any other questions.

Comments and questions:

Mr. Vandersmissen made remarks on behalf of the vaccine manufacturers of industrialized countries.

- The vaccine industry does not need further convincing that VVMs serve a purpose.
- Each issue is more or less important to individual companies.
- Concern is due to the disconnect between what VVM was and seems to be now in the effort to address regulatory issues. Originally there was a correlation between VVM response and potency. Industry wants such a correlation. Therefore, we are making a plea to find a VVM that would do this. There is also a need for public/private partnership. WHO should ask for proposals for a “more perfect” VVM indicating the remaining potency of the vaccine.
- Also, there is a regulatory question. WHO has inquired and stated that regulatory approvals are not needed. We find this surprising, but will be happily surprised if true. There is a need to clarify if regulatory authorities in Western countries will demand certain things. We also need validation standards to validate VVM performance. The regulatory authorities may be tolerant, but that is not the norm.
- The VVM tells of exposure to heat and manufacturers are responsible for potency. There are circumstances where the present VVM will not match the condition of the vaccine. The VVM will not register freezing for instance. Also, there is a tolerance of shelf life and expiry. The vaccine may be OK and the VVM not OK. Also, are we sufficiently certain that brief exposures to high heat will not be shown by the VVMs, but might harm the vaccine? There is a liability issue. Manufacturers take responsibility for vaccine provided it has been well stored, and need a liability disclaimer that says that the VVM is something we do at a customer’s specific request.
- LifeLines is a sole supplier. They have a significant responsibility to supply VVMs. Also it is important that standards set today do not prevent something better to evolve. Some manufacturers are already content with regulatory/liability issues, but others may not be.
- VVM development was carried out without the rigor of the pharmaceutical world, e.g., GMP conditions. Manufacturers have been told by LifeLines, however, that progress with GMP has been made.
We are also puzzled that if LifeLines is so indispensable and VVMs are so desirable, then why doesn’t PAHO also want VVMs? Therefore, we make a plea for standardization in this mass market as much as possible.

Also, implementation means time and cost for investment by vaccine manufacturers in terms of equipment and management. We are not opposed, but want conditions to implement in the best possible way. Some companies are more prepared than others (e.g., those who have VVMs on polio vaccine). Disparities between companies come from the fact that there are “late joiners”.

Additional questions raised follow:

**Question:** With new specifications, the lower endpoint is now 5°C. Would like to know more about the reasons why 5°C replaced the 8°C specifications in the document.

**Question:** Has a technique to measure the potency prior to use been explored?

**Question:** Three machines for labeling are mentioned in the meeting folder. We need to put VVMs on the neck of ampoules. Japan BCG used a machine developed in Japan to do this. Is the piggyback machine used for ampoules or just for vials? The ampoule neck is very high and it is hard to imagine technically adhering a VVM to a neck of an ampoule without breaking it.

**Question:** If the VVM manufacturer has a supply problem and the vaccine manufacturer cannot receive VVMs, who is responsible?

**Question:** Does the VVM show the freeze cycle in OPV?

**Question:** Regarding the new test procedures, testing should be performed in 10-15 days following the receipt of sample VVMs. If VVMs are to be kept at -20°C in a freezer, then why cannot testing be performed at any time?

**Concern:** We are measuring the difference between active squares between batches. In documents WHO says that it should be ±0.03, but we sometimes get ±0.06.

Dr. Kartoglu thanked all contributors and mentioned that all these questions will be addressed under appropriate sessions.
“Without VVMs I could never be sure what happened to the vaccine before it came to the health center”.
Health worker from Kenya
Regulatory Considerations

When OPV VVMs were implemented, WHO did reassessment visits to manufacturers and various regulatory authorities, discussed the VVM issue and provided a VVM information packet. Regulatory authorities have been aware of VVMs since 1996. The need for regulatory oversight has not come up as an issue with OPV VVMs, but now some concerns have been raised. Therefore WHO has decided to accelerate contacts with regulatory authorities including those related to the suppliers of large quantities of vaccine to the UN system. The findings can be summarized in Table 2.

Table 2. Regulatory considerations on VVM implementation on all vaccines, responses from National Regulatory Authorities

<table>
<thead>
<tr>
<th>Region</th>
<th>Country</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>India</td>
<td>Notification to regulatory authorities needed and some attention required during routine GMP inspections as for any other item related to packaging and shipping and transport.</td>
</tr>
<tr>
<td></td>
<td>Indonesia</td>
<td>Notification to regulatory authorities needed and some attention required during routine GMP inspections as for any other item related to packaging and shipping and transport.</td>
</tr>
<tr>
<td>Europe</td>
<td>Belgium</td>
<td>No regulatory approval required for vaccines that are exported, but would be subject to checking during GMP inspections and would like to be notified of VVM implementation.</td>
</tr>
<tr>
<td></td>
<td>France</td>
<td>No regulatory approval required for vaccines that are exported, but would be subject to checking during GMP inspections and would like to be notified of VVM implementation.</td>
</tr>
<tr>
<td></td>
<td>EMEA</td>
<td>Awaiting response</td>
</tr>
<tr>
<td>America</td>
<td>USA</td>
<td>If the vaccine is not licensed for US distribution, the exportation must comply with the regulatory requirements described in Sections 801 and 802 of the Food, Drug and Cosmetic Act (21 CFR 381 and 382) which refer to export provisions. If specific vaccine as labeled is licensed for distribution in the US, manufacturers need a supplement to their license application. The exact situation of vaccine for UN market needs further clarification with USFDA. USFDA advises US manufacturers implementing VVMs to contact the agency directly.</td>
</tr>
</tbody>
</table>
**Question:** Can you explain more about 381 and 382?

**Answer:** 381 refers to general procedures for exported products. 382 deals specifically with exported products that are not approved. However, on both sections, further advice is needed from the FDA.

**Comment:** Dr. Oliva commented on PAHO’s position on VVM implementation: they have not accepted VVMs so far, because they were available only for OPV and polio had already been eradicated in Americas. They are revisiting this position. Before they take the decision, regulatory issues (country where VVM produced, country where vaccine produced, and receiving country) need to be checked. PAHO will explore the positions of the regulatory authorities in the Americas. PAHO’s delay was due to their wish that all vaccines should have VVMs. All technical information with regard to the use and interpretation of the VVM must be provided to countries. Also, countries must agree to the added expenditure. PAHO is also considering training needs. All these questions must be answered, then PAHO will probably accept vaccine with VVMs.

**Question:** Do you have any information about the countries’ interest in accepting VVMs in PAHO region?

**Answer:** This information is not yet available.

**Question:** We see from the first presentation that some vaccines have arrived with VVMs in Colombia and Cuba. What was the response?

**Answer:** Dr. Oliva responded that he is not aware of that information.

**Question:** The issue of the USFDA will be very important to understand. If WHO advises that UNICEF should take on the liability of the vaccine under export provisions, then buyers would make sure that appropriate regulatory processes are taking place. UNICEF could not accept that.

**Comment:** FDA told us that VVMs would be regulated under the export provisions. The export provisions clearly say that FDA will provide no regulatory oversight in this case. We cannot prequalify manufacturers under these conditions.

**Question:** What are WHO’s plans to approach other regulatory authorities?

**Answer:** WHO will include this information in the action points for the meeting. It is important, however, that the vaccine manufacturers themselves contact the regulatory authorities so that discussions can occur on a case by case basis. WHO can be involved in the discussions, if helpful.

**Comment:** Thimerosal is an issue. Italian authorities told Chiron that thimerosal-containing products can only be exported, similarly with whole cell pertussis. So we could assume that if the authorities want to be involved, it would be under the export provisions.

**Comment:** We are grateful for the steps taken. However, we also feel a need for some measures with regulatory authorities in recipient countries.

**Comment:** All NRAs in developing countries and even in developed ones, have never objected to VVMs when they were attached.

**Question:** When WHO contacted the authorities, did they ask what the responsibilities of the vaccine manufacturers versus the VVM manufacturer were?

**Answer:** WHO didn’t address it in this way. The question that WHO posed was if they would require approval by the NRA.
**Question:** Would it be possible to openly make reference to WHO’s information when approaching our NRAs rather than restarting the process?
**Answer:** WHO will make this information available.

**Question:** What information is available from LifeLines about their next steps for regulatory review of their product, for example as a device?
**Answer:** LifeLines will agree to study any process with WHO and each manufacturer, if it is useful.

**Conclusion:**

It was agreed that it is the vaccine manufacturer’s responsibility to contact national regulatory authorities, with assistance from WHO and LifeLines as required.

**Action Points with regard to regulatory issues:**

1. WHO will continue to informally contact regulatory authorities and will follow up with those already contacted. WHO will share the resulting information with vaccine manufacturers.

2. It is the responsibility of vaccine manufacturers to formally contact regulatory authorities in their countries, with assistance from WHO and LifeLines as required.

3. WHO will address the issue of whether regulatory review is required for countries receiving vaccines with VVMs.

4. PAHO will explore the positions of regulatory authorities in the Americas with regard to acceptance of VVMs on vaccines.

**Liability Considerations**

The risk of VVM failure at field level is very low because their quality is assured by the following procedure:

- Validation by the VVM manufacturer
- Validation by the vaccine manufacturer
- Lot by lot testing before release by the VVM manufacturer
- Lot by lot testing before acceptance by the vaccine manufacturer
- GMP audits of the VVM manufacturer by vaccine producers

The vaccine manufacturer is responsible for the product it releases to the market and for transportation to the country using monitoring devices, of which the VVM is one. Once accepted by the buyer, the responsibility for the appropriate handling, transportation and storage of the vaccine is transferred to the buyer. With VVMs, the potential for unnoticed exposure of vaccines to inappropriate temperatures will diminish, with concomitant decrease in liability risks. Since VVMs are subject to strict controls before use, it is very unlikely that a faulty VVM lot will reach the field. However, if this happened:
- the VVM would reach end point earlier, and the vaccine would be disposed of resulting perhaps in wastage, but no increased liability.
- the VVM would fail to reach the end point in time, with the potential risk of using a heat exposed vaccine. This is the only scenario where a potential liability exists. However, it should be noted that in six years of experience and over 10 billion doses corresponding to more than 500 million VVMs used, it has never been documented that a faulty VVM lot has led to the use of vaccines of unacceptable potency.

**Comments and questions:**

**Comment:** All issues of liability related to the VVM also apply to the vaccine itself. Neither the VVM nor the vaccine can be 100% perfect. Liability issues are huge. We must either take the risks as a vaccine producer based on advice of legal departments or not.

**Question:** When a product has an expiry date, you can find yourself in the same situation as when referring to the VVM – vaccine may or may not be good when end point is reached. Liability could be similar. How does industry address the liability with the expiry or is the comparison not valid?

**Answer:** Mr. Vandermissen replied that the industry addresses the liability issue with the expiry “with great care”. He underlined that there are no easy answers.

**Question:** The expiry date is validated by data on potency. The relationship of the VVM to the contents of the vial is a major issue.

**Comment:** When we talk about liability we should dissociate the reading of the VVM with potency. The VVM is not a potency indicator, it is a time-temperature indicator. Also, from the legal point of view, the temperature is recommended (2-8°C) with a given expiry date and that is the legal responsibility of the manufacturer. Chiron considers it their responsibility to choose the VVM category that best matches the stability of the vaccine and to validate the VVM accordingly.

**Comment:** On the question of validation, the comparison with expiry date surely is relevant. The vaccine is still good beyond the expiry date as well as when the VVM reaches its discard point. Both are set conservatively. Validation of the VVM is attempting to show that at discard point, you are well within the period you can safely use the vaccine.

**Question:** One manufacturer has stated that they are not satisfied with validation, implying that the validation is inadequate. Is this correct?

**Answer:** Some validation has taken place. The question is whether it was with some pre-agreed set of standards? Is it good enough? Industry feels there might be a need to do more.

All participants were asked to clearly state the concerns and questions rather than making general comments. It is recommended that the concerns raised with the validation of VVMs be addressed between the individual manufacturers and LifeLines.

**Comment:** Transfer of ownership does not equate to transfer of liability. UNICEF, as the buyer, does not assume liability. Commercial clauses exclude UNICEF from product liability. The liability must remain with the manufacturer or with another UN agency willing to take on liability.

**Comment:** The buyer doesn’t take responsibility for how the product is manufactured, but takes responsibility for handling it at recommended temperatures.

**Question:** Who is responsible of maintaining the cold chain, UNICEF or countries?
**Answer:** Once accepted, the shipment is the country’s responsibility, and responsibility here means that they must maintain product under proper conditions (temperatures).

**Comment:** Manufacturers sometimes need to replace the product if not delivered properly (e.g., conditions not monitored and then a problem is discovered later). For example, this has happened using the 3M MonitorMark. Some VVMs in one part of the box may change differently to VVMs in another part.

**Comment:** This concern is not related to the liability discussion, but is a physics issue. Since VVM monitors temperature exposure of individual vials, and the impact of heat exposure on the vials when they are packed in a box moves from outside to inside, as a result vials may show different levels of exposure to heat depending on their location in the box: the ones closer to the sides being more exposed while the ones in the middle less exposed.

**Question:** The question is, if a receiving country accepts a shipment and later finds out that a few vials have changed color, could they ask for replacement?

**Answer:** This is a contractual issue regarding acceptance procedure.

**Question:** We have raised many examples of possible complaints and liability situations. Vaccines get repackaged in countries and different shades of VVMs are imaginable. We won’t be able to address all these possibilities.

**Answer:** The example is more of potential wastage, than liability. The VVM is a tool that reduces rather than increases liability. The risk of exposure to unacceptable temperatures exists no matter what.

**Question:** We all recognize that there is some liability. It is a fact of life. However, we would like vaccine manufacturers to clarify for what reason they feel that VVMs could make the situation worse, i.e. bearing in mind that the risk of exposure to unacceptable temperatures exists no matter what?

**Answer:** [by Mr. Vandermissen who represented vaccine manufacturers from industrialized countries] It doesn’t make the situation worse. It makes it literally visible. Before the VVM, there was no way of telling if vaccine was heat abused. Now it will be traced. The positive is that vaccine will be discarded, but the negative is that people will want compensation for it.

**Question:** Isn’t there the risk anyway? Isn’t VVM a tool to reduce the use of unacceptable quality vaccines?

**Answer:** [by Mr. Vandermissen] Yes, it may reduce the risk, but it won’t take it away.

**Comment:** We have clear guidance on international packaging and shipment describing three categories of packaging and allowable temperature ranges. The guidelines must be followed.

Ms. Mazur suggested that the manufacturers should raise their concerns in connection with the validation of the VVMs and asked whether this is the crux of the matter. Mr. Vandermissen, on behalf of the vaccine manufacturers from industrialized countries, commented that the basis of the liability argument is that VVMs are taken as measure of potency. They are not. Accidents in the field are a more manageable risk.

**Conclusion:**
Liability issues exist with or without the VVM, and the VVM does not add any additional liability. On the contrary, it reduces the liability of vaccine manufacturers.

**Action Points with regard to liability issues:**
There are no action points with regard to liability/legal issues (see additional discussion on this and action point on page 34).
In six years of experience and over 10 billion doses corresponding more than 500 million VVM used, it has never been documented that a faulty VVM lot has led to the use of vaccines of unacceptable potency.
Validation Issues - Validation of VVMs

presented by Dr. Ümit Kartoglu, WHO/HQ

Dr. Kartoglu reviewed the process of adding VVMs to a product, highlighting points where the VVMs are validated and other quality control tests are conducted. Table 3 explains all steps and procedures involved in VVM application starting from the request by the vaccine manufacturer to VVM attachment to individual vials. For each step, related validation and quality control tests are also indicated (see Table 3 on Page 24).

Dr. Kartoglu also reviewed the minor changes recently made to WHO VVM specifications and test procedures.

With regard to the specification:

1. First, the change in VVM nomenclature in the specification (to VVM2, 7, 14, and 30) was made due to confusion with terminology A,B,C,D, with packaging ratings.
2. The change to a 5°C specification from a 8°C specification was made so that the mid-point, which is a more realistic temperature for storage, is used. However, this does not change the reality of VVM reaction rate at 8°C.

With regard to the test procedures:

1. The test now includes all VVM types, rather than just VVM2.
2. There is an increase in the tolerance level for OD difference readings from 0.03 to 0.04. The primary reason for this was that studies by vaccine manufacturers and independent laboratories had slightly greater equipment temperature variations so the allowable variation was recalculated to be more realistic.

Conformity studies (using the same test procedure as that for validation tests) have been conducted by WHO-contracted independent laboratories to confirm that the product meets the specifications. Dr. Kartoglu showed an example comparing validation of VVM30 by LifeLines and the conformity study by a WHO-contracted lab. Both results complied with specifications and were in agreement. The summary of the report appears in the Q&A document under question #5.

Validation studies are conducted by both the producer (LifeLines) and buyers (vaccine manufacturers) of VVMs.
Table 3. Processes and validation/ quality control (QC) tests performed during VVM implementation

<table>
<thead>
<tr>
<th>Step</th>
<th>Description of the process</th>
<th>Validation and/ or QC tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer's request and approval of VVM type by WHO</td>
<td>Manufacturer's request to LifeLines</td>
<td>Validation and or QC tests for stability data</td>
</tr>
<tr>
<td></td>
<td>WHO review of stability data</td>
<td>Manufacturers have to validate their stability tests</td>
</tr>
<tr>
<td></td>
<td>WHO approval of VVM type based on stability data (communicated to both the manufacturer and LifeLines)</td>
<td></td>
</tr>
<tr>
<td>Validation of VVM reactivity by the manufacturer</td>
<td>Vaccine manufacturer procures necessary equipment (water bath tanks, densitometer and special thermometers, etc.)</td>
<td>Initial validation test conducted at vaccine manufacturer's facility</td>
</tr>
<tr>
<td></td>
<td>Conduct initial validation test</td>
<td></td>
</tr>
<tr>
<td>Determination of VVM position on the vial and approval of the artwork</td>
<td>Vaccine manufacturer provides artwork</td>
<td>Application validation tests conducted at vaccine manufacturer's facility</td>
</tr>
<tr>
<td></td>
<td>LifeLines confirms that artwork is satisfactory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For special applications, validation tests are performed for application (better adhesion, etc.)</td>
<td></td>
</tr>
<tr>
<td>VVM printing/ slitting</td>
<td>Prepare ink base and run pilot press (LifeLines)</td>
<td>Testing of ink base</td>
</tr>
<tr>
<td></td>
<td>Conduct accelerated tests for the ink base</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Run actual printing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Take samples from each master roll for kinetic tests</td>
<td>Kinetic test</td>
</tr>
<tr>
<td></td>
<td>Take master rolls for slitting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Visual check and samples taken for homogeneity test</td>
<td>Visual check and homogeneity test</td>
</tr>
<tr>
<td></td>
<td>Goods to freezer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conduct lot release test</td>
<td>Testing VVM reactivity</td>
</tr>
<tr>
<td></td>
<td>Ready for shipment</td>
<td></td>
</tr>
<tr>
<td>Packaging and shipment</td>
<td>Give sequential numbers and pack in corrugated boxes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Make necessary booking for shipment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inform customer and advise on arrival</td>
<td></td>
</tr>
<tr>
<td>VVM application on vial</td>
<td>Vaccine manufacturer to check the time temperature indicator which is placed on shipping carton, and measure colour of sample indicator</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conduct lot acceptance test using LifeLines Lot Release Protocol and recommended Sampling Plan</td>
<td>Acceptance tests (by vaccine manufacturer on arrival) using LifeLines Lot Release Protocol and recommended Sampling Plan</td>
</tr>
<tr>
<td></td>
<td>Place goods in freezer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apply VVM to label and/ or vial</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Store at specified temperatures as required by type of vaccine</td>
<td></td>
</tr>
</tbody>
</table>
Comments and questions:

The following two questions were given to the secretariat in writing by Mr. R. Jain (Panacea) who had to leave early due to his return flight schedule:

**Question:** Manufacturers are getting VVMs with starting optical density differences greater than 0.06 from one batch to another. The center square of the VVM is therefore “bluish” and this makes the VVM unacceptable to receivers of the vials.

**Answer:** The density difference referred to by Panacea is not the OD difference referred to in the specification, but refers to batch to batch consistency. The starting point of the VVM active surface is never “white”, but should be slightly coloured and could vary from batch to batch. The important point is that the difference between the active surface and the ring is greater than 0.25 OD units. The problem may be due to the fact that early VVM training materials showed a “white” active surface, creating a misperception by users. All new versions of the training materials have some slight colour in the start point of the inner square.

**Question:** VVMs tend to remain at Stage 3 at storage at 2-8°C and did not reach Stage 4 even after 1 year.

**Answer:** VVM color changes do not jump from stage to stage; it is a process which moves gradually. Vials should be discarded when the VVM reaches Stage 3.

After responding to the written questions from Panacea, Dr. Kartoglu moved onto the new questions/concerns raised during the morning session:

**Question:** Why do you have to start the validation study within two weeks of receiving the samples since the VVMs are stored at -20°C.

**Answer:** The test procedure was first designed for the independent laboratories contracted by WHO and that is where the two weeks come from. Vaccine manufacturers can begin their studies when convenient.

**Comment:** VVMs do not record freezing temperatures.

**Answer:** This is correct. However, it should be noted that VVMs are indicators of heat exposure, not freezing. It is unfair to expect the VVM to do more than what it is designed for.

Dr. Prusik responded to “consistency” issues. We all have a common mission to provide high quality vaccine to the point of use to prevent vaccine preventable diseases. LifeLines wants to work openly and transparently with the vaccine manufacturers. LifeLines prides itself on its demonstrated progress in quality over the last several years and in its continuing quality improvement initiatives. This commitment is emphasized in our current Quality Policy of 12 February 2002. The evolution of our Quality Management System began with management’s decision in September 1999 to become ISO 9001:1994 registered. This commitment resulted in the successful registration of our company by SGS International Certification Services, Inc. in March 2001 (Certificate Number: US2001/2459). A surveillance audit was completed by SGS in September 2001, with registration being maintained. The quality system currently registered is compliant with the FDA quality system requirement (QSR) under 21 CFR 820. Such a commitment is consistent with the rationale provided relating cGMP to ISO standards under 21 CFR 210/211 during its proposal phase (May 1996). The Company has demonstrated its increasing commitment to improving the quality system by now taking two key steps.

- First, to become ISO 9001:2000 registered in May 2002, Lifelines will be committing to specific performance metrics that are required by the new revision and generally consistent with the position of the FDA regarding process control and cGMP.
- Second, the system will be further refined to enhance cGMP compliance by June 2002.
The Company has developed its “open door” and transparent attitude and is delighted to cooperate with any vaccine manufacturer in the examination and improvement of its quality system, and also to organize any visit to the facilities to provide information and training on all aspects of VVM function, use and implementation. GSK and Aventis Pasteur recently audited LifeLines, with few comments.

Dr. Prusik further explained the manufacturing process and polymer colour reaction and how LifeLines treats every lot for release. LifeLines monitors storage conditions in storage freezers and water baths with thermocouple monitors. Due to the inherent variability of densitometers, based on practice, the allowable variability was increased slightly in the specifications. LifeLines uses computer interfaces with their densitometers and flatbed scanners to reduce release times.

Dr. Prusik graphically explained the need to control temperature during testing in water baths. Slight differences in temperature dramatically affect results.

![Temperature Dependence of VVM30s](image)

**Figure 3. Temperature dependence of VVM30s (days to end-point), LifeLines**

As seen in Figure 3, even a slight change of 0.5°C in temperature will skew the days to end point by approximately 2 days.

Finally, Dr. Prusik showed a graph of number of customer complaints versus time, January-June 2000 through present. Complaints have decreased from 24 from January-June 2000 to 3 from July to December 2001 to 2 in the most recent time period (January-March 2002). Most of these complaints are related to normal label issues (e.g., die cut depth, text registration). Dr. Prusik concluded his remarks by inviting manufacturers to visit and audit LifeLines Technology.

**Question:** What is the humidity effect on VVMs?

**Answer:** There is a slight increase in reactivity at lower humidities.

**Question:** Validation is a process that provides assurance for the user that the monitoring device has been tested by assessing measurement accuracy and measurement responsiveness. The device’s measurement accuracy and measurement responsiveness need to be defined. Validation should include the defined range over which performance is expected. These attributes of validation have not been addressed.
**Answer:** Dr. Prusik stated that LifeLines can provide any additional data if needed. Dr. Kartoglu commented that tests are run to see if the product meets defined specifications, which were outlined previously. All test procedures check the performance specifications. It is not clear what information is being requested? Since the VVM reaction is chemical and can be calculated, we do not understand the need for testing VVMs under more temperature points than required by the standard test procedures.

**Question:** In real life the product will not be at consistent temperature and temperature spikes may occur. Therefore Merck wants to see the range of performance. Besides, we should be looking at multiple lots and use a standard sample size.

**Answer:** [by Dr. Martin] LifeLines is a small scientific firm (of 35 people - 5 PhDs and 8 bachelor level scientists) and is very open-minded and transparent. As we know the VVM response characteristics in-depth, LifeLines agrees to discuss this topic with manufacturers who want to test different aspects of the product. LifeLines could use existing data to theorize performance based upon a variety of sequences of temperature conditions and study with manufacturers any test scenario.

**Comment:** Endless scenarios happen in the field. The VVM reaction is a predictable reaction and any scenario can be mathematically calculated. The validation is focused on standard temperatures.

**Question:** Merck would like to see measurement accuracy and measurement responsiveness of the VVMs. Measurement responsiveness can be measured by exposing the VVM to short duration of excessive heat. A temperature profile realistic of temperatures exposed to the product outside of the product storage conditions needs to be investigated.

**Question:** We [Wyeth] also want to see the cumulative effect of up and down temperatures rather than static ones.

**Answer:** LifeLines can address these concerns and can set up a variety of sequences of temperature conditions and can study any test scenario with manufacturers.

Dr. Dellepiane, underlining the concerns raised regarding the peaks in temperature and desire for studies in variable conditions, stated that vaccines for licensing never go through such field tests, and asked whether any vaccine manufacturer have such data for their products. The answer was that these data are not available.

Currently, WHO is conducting a series of vaccine transportation studies in a group of countries. In this study, all four types of VVMs are used to record heat exposures over time. Although the study is not designed to validate VVMs, the findings might be of interest, and WHO can share the data when available.

**Question:** Have there ever been tests done with probes inside and on the vial together?

**Answer:** The difference between the label level and internal vial temperature is minimal. Before considering a new test, LifeLines suggests that we ask two questions: 1) Is there a real interest for public health in doing these extra studies? 2) Is there an interest to ask more of the VVM than you ask of your vaccine? The major manufacturers who have been using the VVMs for years, seem comfortable with the VVM which protects from vaccinating children with vaccine that could have been heat inactivated.

**Question:** We [Vacsera] are a user of VVMs. We have not seen sufficient validation data of VVMs. There is a need to illustrate aspects of quality assurance level and acceptance processing. We need to know about the recording system, and percent of consistency.
Dr. Kartoglu wanted to draw attention to the fact that validation tests are tests conducted by the vaccine manufacturers as users of the product. Therefore, vaccine manufacturers must conduct their own validation to satisfy themselves with the performance of the device. However, as promised by LifeLines, additional data on LifeLines internal validation of all batches can be made available on request. Moreover, if participants are interested to see the full report of the consistency study conducted by Precision Measurements and Instruments Corporation (PMIC) under WHO contract, WHO is happy to share the copies of the report.

Comment: Merck has looked at VVMs for a brief period of time. They are new to VVMs, but are not newcomers to the vaccine field and appreciate the kind offer of LifeLines to share data. There are regulatory requirements that dictate the types of studies to be done. How the vaccine is used in the field will affect the meaning of the indicator and how it is validated. The concept of VVMs is a very valid, a good one. It is an important public health tool. We are not denying that, but want to see what the needed additional data might be.

Answer: We need a correction here. Our understanding regarding USFDA regulatory requirements is that there may not be any regulatory approval required. Today, we do not know if any extra data are required for regulatory considerations. At this point there is no need for such data for regulatory reasons and it is not correct to mention that such studies are dictated by regulatory requirements. There is no proof for this.

Comment: Given that USFDA regulatory requirements might exist, Merck is looking for data just in case.

Since no clear response was given, Dr. Kartoglu repeated the question about whether we have any data for the heat stability of the vaccine in field conditions and whether any vaccine manufacturer included such data in their licensing dossier? He further questioned whether the “field condition” study of VVM is asked only for curiosity. Mr. Vandermissen responded that in general you do not need to collect such data, but it can be added to the file as manufacturers see fit. Dr. Dellepiane stated again if the feeling of the group here is that additional studies were needed, a comprehensive protocol could be developed.

Comment: The test procedure responds to the technical specifications that have been available since 13 August 1999 and have been discussed in several meetings and have been sent to vaccine manufacturers for their feedback. These specifications and test procedures were not created yesterday. The only changes in the revised versions are very minor and were outlined earlier today. If you still believe something else needs to be validated for VMM, we would like to hear it very clearly. The current specification and protocol have been subjected to much review and have been reviewed by vaccine manufacturers again and again. If we need to add something, then we need to add it, but we haven’t heard anything in particular that needs to be added. The current specification is the lowest common denominator validation process right now.

Comment: Most of us agree on the quality control testing that has been happening. On the matter of validation, there may be scattered suggestions.

Comment: Whatever validation was done for polio VVM, the same was done with other VVMs. The process of testing the VVM types is the same as what was done for polio.

Question: Are there really specific issues about the process being used for validation?
**Answer:** As long as we do not have information from our authorities, Chiron does not see any necessity for additional changes.

**Answer:** Merck would like to see the following: Lot consistency (at least 3 lots should be tested for each reaction rate category), validation performed against a defined validation standard, an appropriate sample size according to a sampling procedure, measurement accuracy, measurement responsiveness, the effect of humidity on VVMs, testing correlation between each VVM reaction rate category to all vaccine stability profiles that require VVMs (this includes multiple lots to analyze consistency of vaccines and VVMs and an appropriate sample size, and a test analyzing the VVM reaction rate category exposed to an ambient temperature profile realistic of a cold chain break (not a static test).

**Comment:** The issue is that specific manufacturers have needs that must be met and can do those tests themselves or working with LifeLines. WHO has financed work to set specifications and conduct conformity testing. But if manufacturers need to do additional testing, they need to approach their own regulatory authorities, and make a determination.

**Question:** Addition of relative humidity and equipment details are new to the test procedure. We will have to test the samples under these conditions and that will take some time.

**Answer:** Relative humidity is not new, it was also one of the conditions in the previous version of the test procedure. It is correct that the new version makes a clear reference to equipment that is important for compatibility of the results. However, we know that all vaccine manufacturers conducting validation tests are using the equipment as specified in the new test protocol. We do not see any problem here.

**Conclusion**

Specifications and test procedures have been defined and no changes were suggested. Validation is the responsibility of vaccine manufacturers and is analogous to the validation of all other raw materials used in their production.

**Action Points – Validation Issues**

Validation of VVMs is the responsibility of the VVM supplier and vaccine manufacturers.

1. Validation and conformity studies should follow the standard test procedures (E6/PROC/5 dated 25 March 2002) and product specifications (E6/IN5 dated 25 March 2002).

2. Some manufacturers may need additional testing to meet internal or national regulatory authority requirements. LifeLines offered to work with individual vaccine manufacturers to study any additional testing that could be of specific interest to their vaccines.

3. WHO will share the PMIC laboratory report with any individual who is interested.
“You know what others cannot see if they do not have VVM.”

Health worker from India
Dr. Kartoglu outlined labeling and application strategies for the full custom label and dot. Among all applications, the neck of the ampoule is the most difficult one. Japan BCG has successfully implemented this application. Chiron has also successfully implemented top labeling.

Table 4. VVM Labeling and application strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Presentation</th>
<th>Full label</th>
<th>Dot application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage</td>
<td>Liquid and freeze-dried</td>
<td>-20°C prior to</td>
<td>Piggyback machine to apply dot onto custom label</td>
</tr>
<tr>
<td>Application</td>
<td>Liquid vaccines</td>
<td>Same as common label</td>
<td></td>
</tr>
<tr>
<td>Freeze-dried vaccine in VIAL</td>
<td>Not applicable</td>
<td>Top labeling machine</td>
<td></td>
</tr>
<tr>
<td>Freeze-dried vaccine in AMPouLE</td>
<td>Not applicable</td>
<td>Special applicator head for on-line applications</td>
<td></td>
</tr>
</tbody>
</table>

Mr. Nagashima (Japan BCG) gave a presentation on VVM implementation. Japan BCG first learned about VVMs in March 1998 from WHO. By February 2001, Japan BCG ordered VVMs and in August 2001, vaccines with VVM were shipped to countries through UNICEF. The major difficulties were due to the shape of the ampoule and the need to attach the VVM to the neck. Japan BCG sells only BCG. Difficulties were overcome by close collaboration with LifeLines and the machine manufacturer. A special labeling machine was made to fit the specification of the ampoule.

In the beginning, they encountered the following problems:

- The labeling machine speed maximum was 150/min.
- The VVM tended to peel off sometimes after labeling.
- The liner easily broke off during labeling.

To overcome these problems they:

- installed the point sensors of the labeling machine to maximize performance,
- installed a device which adds additional pressure on the labeled VVM to strengthen adhesion to neck of ampoule,
- added adhesive to VVMs,
- used polyester instead of a Kraft liner, and
- changed the shape of the VVM from an oval to a rectangle to avoid overlapping of the end parts of the VVM.
Implementation was hard, but Japan BCG understands the importance of compliance.

Dr. Friederich (Chiron) showed samples of OPV tubes with VVMs on caps. For freeze dried vaccines, Chiron looked for a flip-off top that would accept a label and found a supplier. Then Chiron invented a machine to apply labels at an industrial speed. Today, they run labeling equipment at 400 vials per minute, so VVM application is not slowing down their process. They wanted to take advantage of LifeLines’s knowledge of VVMs, but not their normal labeling. So they worked with their suppliers to develop a piggyback process. They have qualified a new label supplier, so Chiron is in full control of the label. It was not that difficult. It was not inventing the wheel, simply putting the pieces together.

Now Chiron can order as few as 50,000 VVMs and apply them on whichever label they want which gives quite a bit of flexibility.

Dr. Martin thanked the two companies and mentioned that these are examples of good collaboration between LifeLines and the companies.

**Comments and questions:**

Dr. Ahun highlighted the fact that all applications are feasible, whether on the neck of the ampoule or the cap of freeze-dried vaccines. Dr. Kartoglu suggested that LifeLines should continue working closely with vaccine manufacturers to identify the best solution for application.

Once the VVMs have reached the country, a flow of information back on vaccine wastage is going to be an important logistic issue for countries. This monitoring needs to take place. UNICEF SD mentioned a new tool, the Vaccine Arrival Report, which began to be implemented in limited countries in 2002, could be a mechanism for reporting.

**Action Points – Logistics**

LifeLines should continue working closely with vaccine manufacturers to identify the best solutions for label application.
The last session was devoted to any other business not covered in previous sessions. The floor was opened for questions.

Comment: UNICEF SD would expect terms to handle the sole source issue that UNICEF would be comfortable having themselves. We have to have symmetrical commercial relationships since UNICEF is asking manufacturers to deal with a single commercial entity. For example, in the case of minimum ordering quantities, if LifeLines said the order was too small, then UNICEF can not ask for such a small quantity from the vaccine supplier.

Answer: The minimum order quantity issue is solved now. The minimum order we can make is 500,000 for a full label VVM. That is why we developed the dot label and piggyback machine option so that any order size can be handled. The cost of shipping will make small orders very expensive. But LifeLines is ready to consider any exception, for example joint shipments.

It was further commented that there is a standard set of packaging to ensure quality of the product and with smaller quantity orders, packaging and shipping costs might exceed the value of the shipment. The most dramatic example was given as countries receiving VVM samples for a field study: 240 VVMs in an envelope with 20 kg dry ice in a shipping box. In some cases with small quantities of vaccine orders, shipping costs become higher than vaccine costs.

Dr. Prusik showed a graph outlining the increase in capacity of LifeLines to produce VVMs in a single shift per day from 1998 (150 million VVMs per year) to 2003 (1 billion VVMs per year). Dr. Martin further commented that the current number of VVMs required for the industry today is estimated at 167 million per year. However, the current capacity of LifeLines is more than 600 million per year using only one 8-hour shift. The capacity in 2003 will be 1 billion on a single 8-hour shift.

Mr. Jarrett noted a lot of work had been done around polio. But, the polio demand for VVMs would probably decrease and other complexities in demand in other products would emerge. Ms. Hall also mentioned that the business model for polio VVMs and other VVMs differ. For the latter this means lower quantities for each antigen and possibly smaller production runs.

Comment: As a vaccine supplier, LG Chemical is willing to do anything. If WHO decides, we will follow. In this case, there is only one issue. LifeLines is the only supplier. The rule of demand and supply does not work in this case. It is a supplier’s market. The vaccine price decreases every year. Our problem is that there are no competitors in VVMs.

Answer: If you look at the history paper (provided in the folders), there were more potential suppliers of VVMs, but they could not compete in price. Other companies failed to develop an adequate product. WHO does continue to work with these companies, but there is little move from them to make something. When we are dealing with an issue that has a high importance for the lives of children, we do work with sole suppliers. There are vaccine suppliers in this room who fall under the “sole-supplier” category for certain products UNICEF, GAVI, or even their own...
national health agencies purchase. We always deal with sole supplier issues. I do not believe that vaccine prices are decreasing.

Mr. Jarrett concurred that we have lost vaccine producers and prices are increasing. There is tremendous concern about the exit of manufacturers from basic vaccines and shortages of supply. We have to listen to manufacturer's concerns and do not want to place undue constraints on them. UNICEF plans to visit not yet pre-qualified manufacturers to discuss commercial issues with regard to these traditional vaccines. In his concluding remarks, the Deputy Director of UNICEF Supply Division recommended that an action point be established per the following: “Each manufacturer to contact their legal office to review liability and to come back with any specific issues that may hinder VVM implementation.”

Chiron endorsed working on public/private partnership to move VVMs forward.

### Action Points - Other

1. WHO will collect feedback from the field on vaccine management to document to impact of the VVM and will share the data with interested parties, including vaccine manufacturers.
2. Each manufacturer to contact their legal office to review liability and to come back with any specific issues that may hinder VVM implementation.
Dr. Ahun concluded the meeting, stating that by the end of 2002, there is a hope VVMs will be available on all vaccines as promised to program managers.

Dr. Milstien thanked the meeting organizers. Dr. Milstien said that the meeting is a milestone in that it has resulted in responsibilities for all parties, which should be taken very seriously. The public sector made a promise, and that promise has not been fulfilled. Dr. Milstien especially thanked the vaccine manufacturers that have already implemented VVMs. They should be recognized for their efforts. We need to try to find a way for the other vaccine manufacturers to move forward. As Dr. Ahun said in her presentation adding VVMs is the best thing vaccine manufacturers can do for the children of the world.
"VVM helps me to understand whether there is a cold chain problem."

Health worker from Vietnam
List of participants

Dr Mercy Essel Ahun
EPI Manager, Disease Control Unit
P.O. Box KB493, Accra
Ghana
tel: +233 21 678 078
fax: +233 21 667 980
e-mail: epighana@africaonline.com.gh

Ms Susan Beckert
Merck & Co., Inc.
770 Sumneytown Pike
West Point, PA 19486
USA
tel: +1 215 652 9858
fax: +1 215 652 4896
e-mail: susan.beckert@merck.com

Ms Andrea Berlinger
Berlinger & Co AG
Mitteldorferstrasse 2
CH-9608 Ganterschwil
Switzerland
tel: +41 71 982 8811
fax: +41 71 982 8839
e-mail: andrea.berlinger@berlinger.ch

Mr Derek Booth
TMC Group
Riverside Buildings, Unit 1 Dock Road
Connah’s Quay, Flintshire CH5 4DS
United Kingdom
tel: +44 151 336 6265
fax: +44 151 336 6255
e-mail: Derek@T-M-C.com

Mr Russell Booth
General Manager, TMC Group
Riverside Buildings, Unit 1 Dock Road
Connah’s Quay, Flintshire CH5 4DS
United Kingdom
tel: +44 1244 817 100
fax: +44 1244 818 502

Dr René Bouzinac de la Bastide
Pharmacien, Aventis Pasteur SA
Campus Mérieux
1541, avenue Marcel Mérieux
F-69280 Marcy l’Etoile
France
tel: +33 4 37 37 3462
fax: +33 4 37 37 3865
e-mail: rene.bouzinac@aventis.com

Mr Alan Brooks
Program Officer
Bill & Melinda Gates Children’s Vaccine Program (CVP)
Program for Appropriate Technology in Health
Centre d’Aumard
55, avenue Voltaire
Ferney-Voltaire 01201
France
tel: +33 4 50 28 0963
fax: +33 4 50 28 0407
e-mail: abrooks@path.org

Mr Chris Caulfield
Lifelines Technology, Inc.
116 American Rd.
Morris Plains, New Jersey NJ 07950
USA
tel: +1 973 984 6012
fax: +1 973 984 1520
e-mail: chrisc@lifelinestechnology.com

Dr Tae-Hong Choi
General Manager, Pharmaceutical Business Unit
Cheil Jedang Corporation
10F, Cheil Jedang Building
500, 5GA, Namdaemoon-No Chung-Ku
Seoul 100-095
Republic of Korea
tel: +82 2 726 8410
fax: +82 2 726 8429
e-mail: 040100@cj.net

Dr Dario Cresci
Technical Director, Rosia Plant
Chiron
Via Fiorentina 1
53100 Siena
Italy
tel: +39 0 577 243 662; 243 987; and 243 979
fax: +39 0 577 243 703
e-mail: dario_cresci@chiron.it

Mr Willem Dikker Hupkes
Introtech
Hoofdweg 73
7371 AE Loenen
Netherlands
tel: +31 55 505 8383
fax: +31 55 505 8333
e-mail: hupkes@warmmark.com
Dr Jackie Fournier-Caruana  
Scientist, ATT  
tel : +41 22 791 2974; fax : +41 22 791 4384  
e-mail : fourniercaruanaj@who.int

Dr Elwyn Griffiths  
Coordinator  
Quality Assurance and Safety: Biologicals, QSB  
Vaccines and Biologicals Department (V&B)  
tel : +41 22 791 3890; fax : +41 22 791 4971  
e-mail : griffithse@who.int

Dr David Heymann  
Executive Director  
Communicable Diseases, CDS  
tel : +41 22 791 2212; fax : +41 22 791 4752  
e-mail : heymannd@who.int

Dr Ümit Kartoglu  
Technical Officer, ATT  
tel : +41 22 791 4972; fax : +41 22 791 8384  
e-mail : kartogluu@who.int

Ms Ulla Kou  
APo, VAM  
tel : +41 22 791 4289; fax : +41 22 791 4210  
e-mail : kouu@who.int

Dr Julie Milstien  
Coordinator  
Access to Technologies Unit (ATT)  
Vaccines and Biologicals Department (V&B)  
tel : +41 22 791 3564; fax : +41 22 791 4384  
e-mail : milstienj@who.int

Ms Anne Mazur  
Legal Office  
tel : +41 22 791 2685; fax : +41 22 791 4158  
e-mail : mazura@who.int

Dr Pem Namgyal  
Medical Officer, EPI  
tel : +41 22 791 2617; fax : +41 22 791 4193  
e-mail : namgyalp@who.int

Ms Emma Uramis  
Technical Officer, ATT  
tel : +41 22 791 3579; fax : +41 22 791 4384  
e-mail : uramise@who.int

Mr Michel Zaffran  
Programme Manager  
Vaccines and Biologicals Department, V&B  
tel : +41 22 791 4373; fax : +41 22 791 4227  
e-mail : zafffranm@who.int