How far you can push the envelope, how much can you use VVMs to take vaccines out of the cold chain?

Julie Milstien *

When I was hired by the WHO in 2001, I became the focal point for VVMs. But the story with VVM goes way back to 1979. Where were you in 1979?

In 1979 I was working for the Food and Drug Administration (US) and wasn't involved with WHO at all. My first involvement was in 1983 when I was working for PAHO and I went down to Peru and there I saw the prototype VVMs that were on measles vaccine.

Did you take part in that study?

No, no I didn't. I was working on vaccine storage issues because we were looking at potency testing and I wanted to have it on video to document the conditions vaccines were being exposed to, and I went to Iquitos, Peru, and we saw them, I guess it was the regional store there, doing the field test on the prototype indicators.

When I came in - I think Michel (Zaffran) and Peter (Evans) came about the same time - and Peter was mostly working at that time on the auto-disposable syringes - that was what he came to WHO from UNICEF for - and John - there was work already on the VVMs, but I wasn't really directly involved in them until early 1990s. It was the time we started to discuss with UNICEF. By that time there were three manufacturers...

VVM manufacturers you mean?

Yes, VVM manufacturers. But they dropped out fairly early. 3M was the last one to drop out.

What were the issues on VVMs when you got involved?

When I was involved we had really two challenges. One was to convince UNICEF that this was going to be a good thing. And the second one was to make sure that the specifications were reasonable. Polio was the first start to go forward with UNICEF.

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Around that time we were working with the Children’s Vaccine Initiative which started, I think, in 1991, and the idea of the Children’s Vaccine Initiative, if you remember, was to get a thermo stable liquid vaccine that was given orally that would be against all the diseases of childhood. And so, my part of it was to work on a thermostable polio vaccine. And so we were working very, very hard on trying to get a thermostable polio vaccine and we actually got a thermostable polio vaccine or a polio vaccine that was stabilized with deuterium oxide. At that point, I guess, UNICEF had just agreed that we could go forward with VVMs on polio vaccine and so, at that point, EPI decided, well, we really didn't need a more thermostable polio vaccine because we had VVMs, and if we could use VVMs we really wouldn't need more stable vaccines. And so the project died and it was very painful and we lost credibility with the manufacturers that were working on it.

But, anyway, that's the way it went. Our challenge then was to try to develop the VVMs so that we would know what would be the temperature ranges and that whole work on specifications was way beyond my capabilities - at the time John was bringing that forward - but one of the things that we decided to do was then to do a couple of experiments to show that the stability of the vaccines actually matched what was happening with the VVMs.

*This is the famous correlation study?*

Yes, the correlation study. That study was actually done by David Wood when he was in the NIBSC. But that was fairly late in the development. I mean, the early part was really trying to come to same page with UNICEF.

**Julie, how do you see the future now?**

I think - and this is what we talked about at TechNet - that there is a lot of work that could go forward now, and on really how far you can push the envelope, how much can you use VVMs to take vaccines out of the cold-chain. I mean that was - from my point of view - the real advantage of the VVMs, to really take advantage of the stability of products. And my challenge to the TechNet - of course, the TechNet felt that they couldn't actually make policy decisions - but my challenge to the TechNet was why not, you know, push WHO to actually make some sort of recommendations on specific vaccines that countries can now use the VVMs to take vaccines out of the cold-chain completely? Hepatitis B, for example. Tetanus toxide, for example - the ones that are most stable, and really start using them that way.

Because what's going to happen - the presentation that I gave to the TechNet that John asked me to do was to look at, first of all, the current products and divide them up and they fell into two groups. The one group was products that were relatively unstable but could be frozen so it wouldn't be damaged by freezing. And the other group was products that were relatively stable - in fact, very stable - that were susceptible to freezing and so, that's the group that you would want to take out of the cold-chain. Although, there's been history with the VVMs of taking even the less stable vaccines out of the cold-chain, like polio. But the new vaccines that are coming along don't fall into that clear-cut group and the other challenge for some of the new vaccines, for example - I think, it's GSK’s rotavirus vaccine - won't even fit into one of the little vaccine carriers because it's so big. And so, there's going to be different challenges that are coming along which is why now is the time to actually start to use the VVMs the best way they can be used.
When a new product comes up, actually who decides at what temperature it should be kept? If it is a very stable vaccine - say more than a year at 20-25°C, is there a way that the vaccine could be licensed with storage recommendations out of cold chain?

Manufacturers are required to present data in their licensing application to support the stability and the dating period that they propose for it. Obviously, if they can, they want to have a product that's as stable as possible and can be stored as easily as possible so they would like to have a product that could be stored virtually indefinitely at 2-8°C but they don't always have that data because it takes a long time to get definitive data. You cannot get it concurrently for licensing purposes, although you can then update it using concurrent data. For most products, products for which WHO already put together the guidelines - that's the ECBS - already put together guidelines - there is a recommended dating period of stability and so they will try to match that. But it's basically the manufacturer. The burden is on the manufacturer to determine what would be the stability of the dating period for the product.

But do you see whether it is ever possible that a manufacturer would come up with a product recommending that the product can be kept out of cold chain?

Well, they certainly do it for drugs! So, if they had the data to support it they might do it. I would doubt it because it would be very difficult for them to get the data to support it over a long enough period of time. But because out of the cold-chain means it could be anything, it could be any temperature so they would only be able to provide data at specific temperatures. They might be able to provide data at 25°C and at 37°C and at 2-8°C and freezing temperature, but they wouldn't be able to provide the whole range of temperature extremes that the vaccine might be subjected to.

Thank you Julie.