EXPERT REVIEWS

Reaching international GMP standards for vaccine production: challenges for developing countries

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Standards for vaccine production have been increasing at a rapid rate. Current standards of good manufacturing practice (cGMP) had been thought to be out of the reach of developing country vaccine producers, many of whom were in the public sector, overseen by unvalidated national regulatory authorities (NRAs). With the advent of the GMP regulations in 1963 and their application to vaccine production, even many industrialized country manufacturers with stringent NRA oversight had difficulties. This article assesses the ability of developing country manufacturers to meet GMP by the only currently available global indicator: WHO prequalification. As recently as 1996, no developing country NRA was considered able to enforce GMP compliance. That number increased to four in 2002 and six in 2006, with a concomitant increase in the number of manufacturers considered to be operating to GMP standards. Examples of the difficulties faced by manufacturers in achieving this are given, as well as implications for the future vaccine market.

KEYWORDS: developing country vaccine manufacturer • GMP • national regulatory authorities • WHO prequalification

Good manufacturing practice (GMP) is a term recognized worldwide for the control and management of manufacturing and quality control testing of foods, pharmaceutical products and medical devices [101]. The US FDA first finalized GMPs for finished pharmaceutical products in 1963 [1], and in the 1970s the FDA expanded these regulations to "…assure that such drug meets the requirements of the [Food and Drug] Act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess" [102].

Later, the WHO developed prototype GMP guidelines to be adopted by all countries for pharmaceutical products [2], which have now been adopted by approximately 100 countries. This document covers personnel, premises and equipment, animal quarters and care, production, labeling, lot release and distribution records, quality assurance, and quality control of starting materials, products and processes. Additional guidelines were elaborated by the WHO with specific reference to biological products [3].

The WHO also outlined the specific responsibilities of national regulatory authorities (NRAs) to enforce GMP for biological products [4], which include the responsibility of the regulatory authority to assure the adequacy of the establishment and facilities, starting material, control test procedures, production processes and product specifications through various inspection and oversight activities.

Most countries follow the WHO GMP guidelines, although some have additional criteria. Since the publication in 1999 of GMPs for active pharmaceutical ingredients [5], these International Conference on Harmonization (ICH) guidelines now apply to countries that are signatory to the ICH (the EU, Japan and the USA) or that have adopted their guidelines, such as Australia, Canada and Singapore.

The main principles of the GMP guidelines as elaborated are to define standard documents (e.g., standard operating procedures [SOPs]) and procedures (e.g., validation of all processes and equipment) that will assure that all steps of a manufacturing and release process and

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all products associated with them are consistently reproducible to result in the desired consistent product. This is particularly important for biological products, such as vaccines, for which the production process, raw materials and control tests may be based on living systems that are inherently variable.

The purpose of this review is to elucidate the progress developing country manufacturers have made in applying international GMP requirements to vaccine production, with an emphasis on specific barriers to progress and the driving forces that have helped bring about change.

Components of GMP

From a manufacturing point of view

Brief history of vaccine production

In the beginning of the 20th Century, public research institutes, public hospitals and universities were responsible for vaccine production in many countries. These institutions were under government administration, such as the NIH in the USA, or they were public–private not-for-profit foundations, such as the network of Instituts Pasteur or the Mérieux Biological Institute. They were a means to allow newly developed vaccines to enter the public domain to be used in the fight against infectious diseases. Often, there were close collaborations among scientific institutions. For example, researchers in the USA and Russia worked together to develop an oral polio vaccine in the 1950s, the rights for which were then donated by Albert Sabin to the WHO for the good of humanity [103]. Transfer of vaccine production 'know how' was frequently made to developing country institutions so that many countries, including developing countries, were able to produce their own vaccines. A network of such institutions established by the Institut Pasteur existed in several developing countries; most of them produced Bacillus Calmette-Guerin (BCG) and diphtheria–tetanus–pertussis (DTP) vaccines as well as the rabies vaccine, antitoxins and antivenins. The WHO promoted a quality control system for locally produced BCG vaccines through a system administered through the Danish Statens Seruminstitut [6]. In Africa, there was local production in Kenya, Tunisia, Algeria, South Africa, Morocco, Nigeria, Egypt and Senegal. In Latin America, most countries produced at least some vaccines for their national immunization programs. In 1997, the WHO estimated that there was vaccine production in 55 countries [7].

Two main factors have been responsible for the decline in numbers of vaccine-producing countries: economic factors relating to the management of vaccine production and the acquisition of new production technologies and the enhanced regulatory requirements for vaccine production, including GMP.

Economic policy widely promoted at the end of the 20th Century, partly as a response to the WHO–United Nations Children's Fund (UNICEF) assessments of vaccine manufacturers [7], proposed privatization of public sector vaccine-producing institutions to enhance their ability to apply new technologies and to manage vaccine production in a cost-effective way. In industrialized countries, many public sector producers became private companies, such as the Institute Sclavo in Italy, Commonwealth Serum Laboratories in Australia, Swiss Serum Institute in Switzerland and SBL Vaccin AB (Sweden). In industrialized countries, there were many mergers to form large multinational pharmaceutical companies, of which the vaccine-producing sector was only one small part. Currently, 70% of the value of the vaccine market is concentrated in three companies: Merck, GlaxoSmithKline and Sanofi-Pasteur [104]. However, in developing countries, many manufacturers remained in the public sector, but their management practices became more rigorous.

Also recommended by the WHO-UNICEF studies [7] was the need to establish GMP compliance and to enforce it through competent, functional and independent NRAs. Some developing country institutions have succeeded in maintaining production in compliance with increasing requirements for GMP standards, and some of these institutions are still state-affiliated, such as manufacturers in Brazil, Cuba and Indonesia, while others are in the private sector, notably in India [8]. These countries have been successful in maintaining vaccine production partly because of a strong political commitment to enforce GMP compliance through their NRAs. A discussion of private versus public sector manufacture is out of the scope of this article. It is important to note that the public sector manufacturers that have been successful have been managed in terms of attention to cost-effective management principles and their countries have placed a high priority on national regulation. Private sector manufacturers, who must compete on the international market, are already aware of the importance of meeting the requirements of credible regulatory authorities.

What does it take to meet GMP?

Compliance with cGMP requires setting up a quality system (QS), which will vary in complexity according to the size of the company. However, there are some basic principles to be followed in terms of design, manufacture, validation, quality control, packaging, labeling and storage. Therefore, if the scale of production is not large enough to support the QS, the economic viability of the company may be at risk.

The QS is established to guarantee that a determined product meets the established specifications. It implies that the production process must follow a standard validated procedure to demonstrate its reproducibility and consistency. Consequently, the staff must be competent and qualified to do their work, facilities must be designed and built in order to carry out production, minimizing the risks of failure to meet standards. A QS system requires the documentation of the production processes, equipment, control testing and staff training to allow potential gaps in consistency to be detected before they impact the quality of the product.

NRA point of view

The aim of the WHO biologicals guidelines for the national control of vaccines and sera is to 'provide general guidelines for national health authorities on quality assurance for biological products … The national authority has the responsibility to confirm that the manufacturer is adhering to the approved standards of good manufacturing practice and to national and other

requirements for manufacture and quality control specific to the product' [4]. The guideline states that oversight will depend on the resources available and whether the product is manufactured locally or imported. It provides for a GMP inspectorate and specifies that a 'manufacturer should provide sufficient information to demonstrate compliance with the principles of GMP including adequate quality assurance,' and specifically defines the roles of inspectors [4].

The WHO's NRA-strengthening activities monitor NRAs for their ability to oversee manufacturing processes and enforce GMP, among other things. The GMP indicator includes the following components, of which the first four are critical [105]:

- Existence of GMP regulations or a GMP code that is equivalent in stringency to the WHO GMP guidelines for biologicals
- Mandate to regulate and enforce compliance to that code
- A code of practice and scheme for inspections
- Appropriate expertise of inspectors
- An established procedure to monitor the inspection process
- Monitoring the onward distribution of product as appropriate

The entire GMP compliance process is reviewed as part of the WHO's NRA strengthening activities, not just once, but on a continuing basis, and in order for a product to be WHO-prequalified, a WHO team must be satisfied that GMP compliance is being assured by the appropriate NRA for the manufacture of that product. This is also checked during the prequalification process through visits to the manufacturing facility by the WHO prequalification team, and on a continuing basis with periodic follow-up visits by the prequalification team.

Evidence that a manufacturer is meeting GMP

In general, the evidence that a manufacturer is meeting GMP rests in the fact that its products are released by a reputable NRA. Even for industrialized countries, there are few reliable indicators on which to base such a rating. Usually, however, countries (or groups of countries) that participate actively in the ICH [106] are considered reputable. For developing countries, the situation is more complex, and the one measure in the case of vaccines is that the NRA has been assessed by the WHO's NRA strengthening group, using the indicators discussed previously [105].

However, the names of NRAs that have been assessed and found functional are not released by the WHO. Thus, they can be determined only by indirect means; that is, if they oversee a manufacturer whose products have been prequalified for purchase by the UN agencies, since a mandatory precondition of prequalification is oversight by a NRA that has been assessed and is functional [9]. This allows a means to develop a minimum dataset of independently evaluated functional NRAs [107].

Because this dataset rests on the WHO prequalification process for vaccines acceptable in principle for supply to UN agencies, it is useful to describe this process. Approximately 20 years ago, the UNICEF Supply Division asked the WHO for advice on the vaccines it was purchasing, similar to the kind of support they received from a Scandinavian laboratory that carried out pharmaceutical product testing for them. Supply Division were using an open tender process for their procurement and wanted to have some way to 'prequalify' products that could be considered for procurement. The result was the process, reviewed by the Expert Committee on Biological Standardization, which depends on the product characteristics and also on its regulatory oversight [10]. The procedure has been updated several times, most recently by an advisory committee of experts convened by the WHO in April 2004 [108].

The purpose of the prequalification assessment is to "verify that the vaccines meet the specifications of the relevant tender, which includes meeting WHO product guidelines, and are produced and overseen in accordance with the principles and specifications recommended by WHO for good manufacturing practice…and for good clinical practice…[108]" It is based on five principles, one of which is "reliance on the NRA of the country of manufacture which meets the WHO published NRA indicators," and a second is 'assurance of production consistency through application of GMP specifications' [108]. A WHO assessment team, which includes national regulatory experts in GMP compliance, visits the facility with representatives of the NRA to ensure that GMP compliance is being enforced for the purpose of prequalification of a product, and periodically during the period of time that the product remains prequalified.

The list of prequalified vaccines is posted on the WHO website each month [109].

Table 1 shows the progress that has been made. Prior to 2002, NRA assessment was not a part of the prequalification process. At present, the list of six developing countries that have successfully overseen the manufacture and release of prequalified products includes Brazil, Bulgaria, Cuba, India, Indonesia and Senegal. By contrast, there are 14 industrialized countries

Table 1. Improvement in ability to meet good manufacturing practice in developing countries.

Year	DCs with functional NRAs (n)	Preq products (n)	Preq products produced in DCs (n)	Products produced in DCs (%)
1986	-	35	2*	5.7
1996	-	50	12*	24
2006	6	73	32	44
2008	6‡	79	39	49

Functionality of NRA measured by WHO assessment, indicated by oversight of prequalified vaccines (see text).
*Note that during this time period the Republic of South Korea was included in the list of developing countries. It is no longer.
‡Pending the strengthening of the Indian NRA as mentioned in the text [110,111].
- NRA assessment was not part of the prequalification process at this time.
DC: Developing country; Preq: WHO prequalified.

overseeing the manufacture and release of prequalified products [107]. These countries are Australia, Belgium, Canada, Denmark, France, Germany, Hungary, Italy, Japan, Korea, The Netherlands, Sweden, Switzerland and the USA. Table 1 also shows the increased proportion of prequalified vaccines coming from developing countries, an indication that manufacturers in these countries, currently numbering 13 (one each except for two in Cuba [The Finlay Institute in Cuba produces bulk meningitis vaccine for finishing by BioManguinhos in Brazil] and seven in India), are producing an increasing proportion of the world's vaccines supplied by UN agencies. Owing to the requirements of the prequalification process, this implies that these manufacturers are meeting GMP requirements, and their NRAs are competent to oversee and enforce this. This indicator is subject to regular reassessment of both the production process and of the NRA function.

Technical obstacles to GMP compliance

Aside from the difficulty of changing organizational culture involved in setting up a robust QS, the experiences below outline some of the difficulties that developing country manufacturers have met and overcome to meet GMP requirements. Most of the changes described in the next sections imposed by the manufacturer were driven by changes in GMP guidelines in the USA and other industrialized countries.

Water for injection

Water for injection (WFI) is used in the pharmaceutical and vaccine industries as a solvent and as a final wash for the product contact parts (e.g., containers, closures, tanks, silicone tubes). Earlier, WFI was manufactured by feeding demineralized water (single pass) into a distillation column. WFI generated by the distillation column was fed to a tank from where it was circulated to the point of use by single pass lines. Testing was restricted to end-point product testing of WFI.

The norms for WFI testing changed substantially when rabbit pyrogen testing was replaced by the Limulus Amoebocyte Lysate (LAL) test and testing for total organic carbon was added to the list. Compliance to these revised norms was not easily achieved by the old regime for testing, and soon this became the single biggest driver for the need to undertake extensive chemical and microbiological testing of WFI at various points in its generation, storage and distribution network, rather than testing one sample at the point of use to achieve consistency for high-quality WFI, as specified in industrialized country guidelines.

Generation systems changed from single still units to multiple columns to increase throughput, reduce entrapment of contaminants and improve the efficiency of generation. Storage tanks changed in geometry from horizontal to vertical, and were fitted with spray balls to irrigate the entire inner surface, and with vents fitted with 0.2 µm-rated filters with heaters to remove condensate.

Distribution systems changed from passive gravity-assisted single pass pipes containing WFI to looped piping maintained at 80°C with the WFI traveling at adequate velocity to create turbulent flow within the pipeline to prevent bio-film formation. The significance of dead legs was recognized and avoided to the limit of existing engineering design. Gasketed joints were avoided and orbital welding became the norm. Surface finish and passivation reduced the impact of piping on water quality.

The battle for compliance did not end here. Despite substantial improvements in the WFI manufacturing process, spikes in endotoxin and microbial count led to greater emphasis on the quality of input water to the WFI still. Gradually, testing began to encompass all the multiple steps, beginning from the receipt of water from the source, its multiple purification steps until it becomes 'purified water', which in turn is the feed water for the generation of WFI.

A specific issue of excursions in endotoxin content in WFI led to the finding that the purified water used to generate WFI was the root cause of spikes of endotoxin. This water was stored in polyvinyl chloride (PVC) tanks, and was neither heated or nor treated. A completely new design, therefore, had to be undertaken, with the purified water being controlled in many ways to get consistently high-quality WFI. The microbiological examination of water in this PVC tank showed the presence of Gram-negative organisms, indicating the possible source of high levels of endotoxins. Since these tanks were not cleanable nor sterilizable, this was thus a potent source of the endotoxin found in WFI.

This resulted in changes in the piping of the purified water itself, similar to what was used for WFI, except that it was circulated at ambient temperature with ultraviolet light as the main microbial retardant. More emphasis was given to the process of deionization, which initially had been a source of microbial contamination. Techniques such as electro-deionization resulted in a need to improve the quality of feed, which in turn required the introduction of techniques such as reverse osmosis and ultrafiltration.

Freeze drying

Freeze drying is used to produce various vaccines and biologicals. In earlier days, this process was not considered to be an element of product risk. However, as greater emphasis shifted to cGMP norms with less reliance on end product quality testing, potential risks associated with freeze drying began to be seen.

Freeze dryers hold a half-stoppered sterile product for a considerable period of time during the process, thus raising their potential for contamination of the product. As freeze dryers are costly equipment, they are not easily changed, but the old freeze dryers were not designed to withstand the process of steam sterilization. The challenge for the manufacturers was to provide an adequate assurance of sterility in this process where the freeze dryers could not be steam sterilized.

Studies were conducted to disinfect the freeze dryer, or lyophilizer, using powerful sanitizers such as hydrogen peroxide. Extensive microbiological sampling demonstrated that the process of disinfection did, in fact, give a sterile environment within the lyophilizer. The choice of disinfectants, their residues and their capacity to affect the freeze dryer components were key issues to be addressed while designing such steps. Therefore, manufacturers ensured that all new lyophilizers had steam sterilization capabilities to simplify the process.

Hot air ovens

Hot air ovens have been used for the sterilization of glass containers. Analysis of the working of traditional ovens fitted with single high-efficiency particulate air (HEPA) filters showed that, after the sterilizing phase, when the contents of the ovens cool, there is a contraction in air within the sterile chamber, creating a negative pressure, which leads to an attempt to equalize to atmospheric pressure by sucking in air. The oven design was modified to ensure HEPA-filtered air was supplied to also keep the oven pressurized during the cooling phase.

Continuous particle monitoring

Continuous particle monitoring in classified (specifying number of particles per cubic meter volume of air allowed) areas is also a requirement that was laid down in the late 1990s. In the older facilities, the number of air changes and the sweep efficiency of the filling areas were set to 20 air changes per hour. The need for regular, dynamic monitoring indicated quantifiable nonconformances in the level of particulate matter. This in turn led to changes in air conditioning design, pressure cascades in clean rooms and the enhancement of clothing design, using nonshedding fabric so as to comply with the environmental requirements of the respective classified area (A,B,C or D).

Autoclaves

Autoclaves have traditionally been used for the sterilization of material. The original concept involved exposure of the material to be sterilized in a chamber with steam to a specific temperature for a specific time period. As concepts evolved, it became essential to monitor the quality of steam to ensure that it consistently had the right characteristics to produce the same kill rate for a given time–temperature relationship.

The deleterious effect of the presence of air pockets in the chamber led to the study and standardization of the load pattern geometry and the use of powerful vacuum pumps to extract air. The issue of leakage and transfer of air into the autoclave during the drying phase was important, especially since vacuum pumps were used to enhance drying. This was a very critical point, as drying followed sterilization and it was possible to recontaminate a sterilized load owing to air leakage. Regular testing of chamber leakage under vacuum led to the need to enhance the door, chamber and valve design to make them leak-proof.

The degree of accuracy required in heat distribution brings up another issue with which older autoclaves cannot comply. Fans within the chamber and cycle control using pressure rather than temperature are features of the new generation of autoclaves. In a few areas, GMP may compel almost all manufacturers to bring in such autoclaves for sterilization purposes.

Major issues

For manufacturers

The greatest challenge for manufacturers has always been to understand the philosophy of the QS concept and implement the cultural change. Frequently, upper management in vaccine-producing institutions poses the biggest barriers to establish GMP, since its importance may not be completely understood. Its establishment may be seen as an unnecessary expenditure, which will increase the cost of production, or the procedures may be put in place to comply with regulations without a full assimilation of the principles. As the facility changes outlined previously are expensive, full management support is necessary.

In developing countries, financing has been a limiting factor to implement and maintain GMP standards. Production and quality control facilities, equipment, heating, ventilation, air conditioning (HVAC) and control systems are very expensive to maintain. It may be difficult to find funds for preventive maintenance, training, calibrations and expensive validations, and many times these activities are postponed, putting the system at risk. Private companies normally have the means to implement GMP, as the costs are included in the commercial price of the product; however, if NRA oversight is not sufficiently strong, some manufactures may be tempted to relax their standards.

Another important impediment in developing countries is to access certified master seeds or those with a traceable history as a starting point for vaccine production. This also holds for cell lines and other critical raw materials such as culture media, stabilizers, adjuvants and, in some cases, vials and other packaging materials, which may impact the stability or safety of the product. Raw materials with international quality accreditations are expensive; most of them are produced in industrialized countries.

Despite these barriers, several developing country manufacturers have been able to obtain regulatory clearance in regulated markets. The Cuban Center for Molecular Immunology has submitted a licensing application for a monoclonal antibody in the USA and Canada, Europe and Japan, and has developed monoclonal antibodies for cancer treatments and organs that have received authorization to undergo clinical trials in the USA. One Indian manufacturer has registered several of its childhood vaccines in Switzerland, and further applications are being submitted. Several manufacturers are requesting or receiving approval from the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme for various products. Others have entered regulated markets in Korea, and are in discussions in the USA.

For NRAs

A review of the WHO indicators for GMP shows that the first of these can be achieved merely by adopting and adapting the WHO GMP guidelines, which were developed for that purpose. Information on a code of practice, how to conduct inspections, and monitoring the inspection process are all included in the GMP training activities offered through the WHO's Global Training Network, which has trained more than 1000 staff since 1996 [9], many of them in GMP. The final indicator, monitoring of onward distribution as appropriate, would not seem to present challenges to a NRA.

However, having a mandate to regulate and enforce compliance to the GMP code has presented a challenge to NRAs, particularly

in the case of public sector manufacturers, where one government organization would be in conflict with another. This has been seen as recently as 1972 in the USA, when the organization at that time responsible for the regulation of vaccines, the Division of Biologics Standards, was also producing vaccines, which were subsequently found to be subpotent, resulting in vaccines then being added to the mandate of the FDA [11]. It was recently documented in India, where three public sector manufacturers were finally closed owing to long-term failure to meet GMP standards under pressure from the WHO. The WHO has recently determined that no new products under Indian NRA oversight will be considered for prequalification, pending strengthening of the Indian NRA [110,111].

In countries where the NRA has not been found functional by WHO, there may be manufacturers meeting GMP. However, without a validation of regulatory oversight, this cannot be sustainably assured. In some of these countries, both vaccine manufacturers and national authorities have questioned the system, arguing that the WHO should provide regulatory oversight for the purpose of prequalification. Some consider the process of NRA assessment an area where the WHO has no mandate. This is why NRA assessment results are not published, and why the process remains voluntary at the request of national authorities.

Furthermore, some argue that when the products are registered in the USA or in Europe, the licensing authorities do the verification, inspection and the oversight of the manufacturing plant, wherever they may be, as an independent activity, as well as all other regulatory oversight. They do not involve the local NRA, except for the fact that the product is licensed in the country of manufacture. However, it should be understood that the prequalification process is not a regulatory process, but a means to ensure that the product meets and will continue to meet specifications for procurement. In addition, it has been a strong driver to ensure enforcement of GMP compliance for manufacturers wishing to sell on the international market.

It may be useful to consider the implications of the demonstration that developing country manufacturers are able to comply with international GMP standards. Some of the more important implications are:

- The increasing need for investment in facilities and process by developing country manufacturers, which could end up by greatly lowering the price differential for vaccines from different sources, even older vaccines;
- The need for developing country manufacturers to offset some of the costs by accessing technologies for more expensive innovative vaccines;
- The current trend towards increasing numbers of vaccines from developing country manufacturers, resulting in a more rapid decrease to the mature product price as competition is enhanced;
- Higher development costs, which may offset the impact of competition, resulting in overall higher vaccine prices.

Expert commentary

The transformation of local vaccine production to a thriving industry composed of manufacturers in both industrialized and developing countries has occurred over the past decades. This transformation has seen the disappearance of most public sector manufacturers; those that remain are expected to meet the same high standards as private sector manufacturers both in developing and industrialized countries. A key driver of this change has been the enforcement of GMP, as indicated both by assessment of NRA enforcement of GMP compliance and by a manufacturer demonstration of ability to work to GMP standards. The developing country manufacturers that have emerged as competitive and GMP compliant will likely be subject to many of the same economic forces that have seen vaccine prices increase in the industrialized world.

Five-year view

5 years ago, the ability of developing country manufacturers to be truly competitive in the vaccine market was in doubt. Yes, they could compete in supplying older vaccines, such as DTP or measles – products few industrialized country manufacturers wanted to supply – and they were even moving into some of the less traditional vaccines, starting with development of hepatitis B vaccine technology in countries such as China, Korea and Cuba, and others such as measles–mumps–rubella, cell culture-based rabies and *Haemophilus influenzae* type b conjugate (Hib)-containing combination vaccines. In addition, independent assessments were beginning to show their ability to comply with international GMP standards. But would they be able to produce truly innovative vaccines? These manufacturers are now accessing technologies for vaccines that are newly in demand in the developing world, such as pneumococcal conjugate and rotavirus vaccines, and some are developing new products against priority diseases of this population. In 5 years time, we expect to see new vaccines for the developing market developed by some of these manufacturers in the final stages of clinical trials. A Cuban manufacturer has developed the first synthetic Hib vaccine. Other manufacturers, notably in Cuba, Brazil and India, are currently working on innovative products for both the developing and the industrialized world.

In addition, in the next 5 years, the use in the industrialized world of vaccine products originating in the developing world will increase. But, as regulatory and research costs increase, price differentials for vaccines from developing country versus multinational producers will diminish. Therefore, there may be an increased need for interventions to insure access to these vaccines to all sectors of the population.

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Key issues

- Vaccine production processes have become more complex and the regulatory environment is becoming stricter.
- The continued compliance with current standards of good manufacturing practice (GMP) requirements has been challenging, even for industrialized country manufacturers, who have restructured and merged to meet these goals.
- Nevertheless, some developing country manufacturers can meet international GMP standards for vaccine production and are competitive on the international market.
- One important factor in this change is the emergence of strong national regulatory authorities (NRAs) in developing countries with the skills, resources and mandate to assure quality production in the facilities under their responsibility.
- A driver for both enhanced GMP compliance and stronger NRAs is the desire of developing country manufacturers to be able to sell vaccines on the international market. To do this, their products must be prequalified, which includes oversight by a strict NRA.
- Vaccine-production costs for complying with international standards of GMP are becoming closer between developed and developing countries.
- One outcome of changes in the vaccine industry is that the number of public sector manufacturers has been decreasing over the last 20 years. The rise in private sector manufacture could impact access to technologies.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Federal Register. Drugs, current good manufacturing practices in manufacture, processing, packing, or holding. Part 133, 28 FR 6385, 20 June, 1963.

• **Invaluable reference for understanding good manufacturing practice (GMP) implications.**

2 Expert Committee on Specifications for Pharmaceutical Preparations. Good manufacturing practices for pharmaceutical products. *Technical Report Series* 823, Annex 1 (1993).

• **Invaluable reference for understanding GMP implications.**

3 Expert Committee on Biological Standardization. Good manufacturing practice guidelines for biological products. *Technical Report Series* 822, Annex 1 (1992)

• **Guidelines provide the analogous information for GMP for biologicals (including vaccines).**

4 Expert Committee on Biological Standardization. Guidelines for national authorities on quality assurance for biological products. *Technical Report Series* 822, Annex 2 (1992).

• **First attempt to define the components of vaccine regulation in general.**

5 ICH Harmonized Tripartite Guideline Q7A: GMP guide for active pharmaceutical ingredients. Final Version. November 2000.

• **Outlines GMPs that are accepted on an international level by signatory countries.**

6 Milstien JB, Gibson JJ. Quality Control of BCG vaccines by the World Health Organization: a review of factors that may influence vaccine effectiveness and safety. *Bull. WHO* 68(1), 93–108 (1990).

7 Milstien J, Batson A, Meaney W. A systematic method for evaluating the potential viability of local vaccine producers. *Vaccine* 15(12/13), 1358–1363 (1997).

8 Frew SE, Rezaie R, Sammut SM, Monali R, Daar AS, Singer PA. India's health biotech sector at a crossroads. *Nat. Biotechnol.* 25(4), 403–417 (2007).

9 WHO. Executive summary of meeting on improving vaccine regulatory capacity, December 2007. *Wkly Epidemiol. Record.* 83(20) 181–184 (2007).

• **Good overview of the principles outlined in this paper.**

10 Expert Committee on Biological Standardization. Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. *WHO Technical Report Series* 760, Annexes 1 and 2 (1988); 771, Annexes 2 and 3 (1988); 786, Annex 1 (1989).

11 Wade N. Division of Biologics Standards scientific management questioned. *Science* 175(25), 966–970 (1972).

Websites

101 Wikipedia. Good manufacturing practice. http://en.wikipedia.org/wiki/Good_Manufacturing_Practice (Accessed 14 December 2008)

102 Immel Resources LLC. A brief history of the GMPs. The power of story telling. Compliance Leadership Series, 2001–2004 http://immelresources.com/ReprintBySubject.html (Accessed 14 December 2008)

103 Albert B Sabin Archives http://sabin.uc.edu/biography.cfm (Accessed 14 December 2008)

104 The Global Vaccines Market 2008–2023 www.reportlinker.com/p096684/The-Global-Vaccines-Market-%20 2008–2023.html (Accessed 14 December 2008)

105 WHO. Vaccine Indicators www.who.int/immunization_standards/national_regulatory_authorities%20/vaccine_indicators/en/index.html/ (Accessed 14 December 2008)

• **These indicators are in the process of being revised; however, their application has provided invaluable guidance to national regulatory authorities working to improve their capacity.**

106 ICH www.ich.org (Accessed 14 December 2008).

107 WHO. National regulatory authorities of countries exporting vaccines through United Nations purchasing agencies http://www.who.int/immunization_standards/national_regulatory_authorities%20/offices/en/index.html (Accessed 14 December 2008)

108 Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies, WHO/IVB/05.19 www.who.int/vaccines-documents/DocsPDF06/812.pdf (Accessed 14 December 2008)

• **Outlines the procedures for prequalification, perhaps the major force for improvement in attainment for developing country manufacturers.**

109 WHO. UN agency prequalified vaccines www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/index.html

(Accessed 14 December 2008)

110 Serum Institute of India, Biospectrum India
http://biospectrumindia.ciol.com/content/BSTOP20/10807112.asp
(Accessed 1 October 2008)

111 Ramachandran R. Vaccine worries. *Frontline* 25(07) (29 March–11 April 2008)
www.hinduonnet.com/fline/fl2507/stories/20080411250700400.htm
(Accessed 14 December 2008)

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