

GMP AND GLP PRACTICES FOR HEALTH RELATED INDUSTRIES WITH EMPHASIS IN BIOLOGICAL PRODUCTS

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First of all, I would like to thank the EMGEN and in particular Dr Sardari for giving me the opportunity to address such a distinguished audience.

As I immediately pointed out to the organisers of this workshop, the International Red Cross and Red Crescent Movement looks, with special attention, at continuous developments in health related industries.

Before telling why, please allow me to present, briefly, the Movement I belong to, which is, as you probably know, the largest humanitarian network of the world.

According to its Statutes - stemming from the Geneva Conventions and formally adopted by International Conferences - it provides assistance to people affected by disasters and conflicts all over the globe.

It has three main components. The first one is represented by the International Committee of the Red Cross (ICRC), the oldest component of the Movement whose humanitarian mission is to protect the lives and dignity of victims of war and internal violence and to provide them with protection and assistance. It has a permanent mandate under international law to visit prisons, arrange for the exchange of prisoners of war, organize relief operations, reunite separated families and undertake other humanitarian activities during armed conflicts.

The second one is represented by the International Federation of Red Cross and Red Crescent Societies (IFRC) which coordinates and directs international assistance following natural and man-made disasters in non-conflict situations.

The main difference between these two Geneva-based-Institutions essentially resides in the reason of the attempt on human lives and dignity. If it results from war or other conflict situations this is an ICRC job, otherwise it is up to the IFRC to intervene.

The third one component of the Movement is represented by 187 National Societies around the world, the real backbone of the Red Cross and Red Crescent. Each National Society, made up of volunteers and staff, provides a wide range of services such as disaster relief, assistance for the most vulnerable people, first aid, training and restoring family links. National Societies also support the public authorities in their own countries as auxiliaries to the governments in the humanitarian field, role which, however, has to be played always maintaining their autonomy so that they may be able at all times to act in accordance with the Principles of the Movement.

All RC/RC activities are carried out according to seven Fundamental Principles which guarantee the continuity of the Movement and its humanitarian work.

The most important of these is the Principle of Humanity which defines the mission of the Movement (to prevent and alleviate human suffering wherever it may be found), recalling its origins (born of a desire to bring assistance without discrimination to the wounded on the battlefield) and double nature (both international and national dimension). The principle of Humanity expresses what the Movement places beyond anything else: the need to act in order to prevent and alleviate human suffering.

Counting nearly 13 million volunteers in 187 countries, the added value of the Movement probably resides in a capillary presence of its network, which makes it able to reach vulnerable people more and more effectively, both in urban and rural contexts.

After this short presentation of the Movement, some of you might think: what does RC/RC has to do with practices for health related industries?

The answer is quite simple: we are interested to such issues because we want to make sure that RC/RC initiatives, carried out according to our Mission, meet the expected result/impact, that is to save as much human lives as possible, safeguarding health conditions of needy people, aim which has been confirmed as top priority in the IFRC 2020 Strategy and ideally summarized by its motto: saving lives, changing minds.

Considering that the use of medicines often represents the best way to prevent and alleviate human suffering in many relief activities, our operational capacity to assist vulnerable people in their own countries essentially relies on the availability of both adequate trained personnel and reserves in cash and kind, including medical supplies, proportioned to the magnitude of the catastrophe/conflict.

The Movement has then paid growing attention to the manufacturing and distribution of **pharmaceutical products**, as defined by the World Health Organisation (W.H.O.)¹.

It has to be pointed out that the components of the Movement may either intervene directly on areas affected by conflicts/disasters or funding the action of other operating entities. In any case, as said above, we want to make sure about the impact of our initiatives and, then, about the quality of pharmaceutical products we distribute or fund.

That is why rudiments of **quality assurance** for pharmaceutical products are relevant in our work, in analogy with other, relatively similar, international bodies, such as the Global Fund. I have to clarify that such rudiments, in principle, do not cover **Good Laboratory Practice** (GLP); in fact we normally do not conduct research activities in this field, even if many National Societies dispose of own chemical laboratories. Directly distributing medicines or funding their purchase, we are more familiar, instead, with **Good Manufacturing Practice** (GMP) - defined as *that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use*.

In my country, Italy, such a function is regulated according to the European Union Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.

This Directive relates mainly to personnel, premises and equipment, production, documentation, quality control and labelling, work contracted out, inspections, complaints and product recalls.

The manufacturer implements an effective pharmaceutical quality assurance system, involving the management and personnel of the various departments concerned.

At each manufacturing site, the manufacturer has personnel with the skills to achieve the pharmaceutical quality assurance objective.

The personnel receives regular training covering the theory and application of quality assurance and GMP.

Hygiene programmes that are adapted to the activities to be carried out must be established. These must include procedures relating to the health, hygiene practice and clothing of personnel.

¹ Any product intended for human use or veterinary product intended for administration to food-producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines.

Premises and manufacturing equipment must also be subject to extremely strict hygiene standards in order to avoid contamination and any adverse effect on the quality of the product.

Moreover, premises and equipment used for manufacturing operations which are critical for the quality of the products must be subjected to appropriate validation.

Production must be carried out in accordance with GMP and must follow the pre-established instructions and procedures. Process deviations and product defects must be documented and investigated.

Technical and/or organisational measures must be taken in order to avoid, in particular, cross-contamination.

For medicinal products, new manufacturing processes and those that have been substantially changed must be validated, and critical phases of the manufacturing process must be regularly revalidated.

The manufacturer must set up a system of documentation covering the various manufacturing operations carried out. These documents trace the history of the manufacture of each batch and the changes introduced during the development of an investigational medicinal product.

The manufacturer must set up a quality control system. This system is placed under the authority of a person who has the requisite qualifications and is independent of production. This person has access to quality control laboratories in order to carry out the necessary examination of the starting materials and packaging materials and the testing of intermediate and finished products. Contract laboratories may be used if authorised.

During the final control of the finished product before its release, the quality control system must take into account the production conditions, the results of in-process controls, the examination of the manufacturing documents and the conformity of the product to its specifications.

Samples of each batch of finished medicinal product must be retained for at least one year after the expiry date.

Member States must set up inspections in order to ensure that manufacturers respect the principles and guidelines of good manufacturing practice laid down by the Directive. They must also take into account Community procedures on inspections and exchange of information.

The manufacturer must ensure that manufacturing operations are carried out in accordance with good manufacturing practice and with the manufacturing authorisation, including medicinal products intended for export. Regular self-inspections must be conducted in order to monitor compliance with good manufacturing practice and, if necessary, to propose corrective measures.

For the purposes of interpreting the principles and guidelines of good manufacturing practice, the manufacturers and the competent authorities must refer to the guidelines set out in the "Guide to good manufacturing practice (GMP) for medicinal products, published by the European Commission.

With regard to medicinal products and investigational medicinal products imported from third countries, importers must ensure that their manufacture conforms to standards equivalent to the good manufacturing practice developed by the Community. Moreover, an importer of medicinal products must ensure that the persons manufacturing these are authorised manufacturers, and an importer of investigational medicinal products must ensure that their manufacturer is notified to the competent authorities and accepted by them.

To place a medicinal product on the market in a Member State, a marketing authorisation must be granted by the competent authority of that Member State or by the

European Agency for the Evaluation of Medicinal Products. The manufacturer must ensure that medicinal products are manufactured in accordance with the information provided in the application for marketing authorisation as accepted by the competent authorities.

For medicinal products, the manufacturer must examine and record complaints regarding a defect. He must inform the competent authority of any defect that could result in a recall or restriction on supply and indicate the country of destination.

After this clarification, I will try to focus my intervention on how this practice has an impact on the work of the Movement and, thereby, on the life of endangered people. As you know, even in normal situation, there are some risks in consuming medicines.

The level of risk can be significant if we consider phenomena such as counterfeited medicines and substandard medicines. Recent W.H.O. figures show that these products - while representing less than 1% of market value in most industrialized countries with effective regulatory systems (e.g. USA, most of EU, Australia, Canada, Japan, New Zealand) - can affect between 10% and 30% of the global stock on sale in many countries in Africa, Asia and Latin America. More recent data, published on the International Journal of Tuberculosis and Lung Disease in 2013, confirm such a scenario by indicating that some 17% of lung-disease-antibiotics on sale in Angola, Democratic Republic of Congo, Ghana, Kenya, Uganda, Tanzania, Nigeria, Rwanda and Zambia are either counterfeited or substandard; this rate lowers in other countries such as India (10%), Brazil and Turkey (both at 4%). What is more, this situation can further deteriorate because of increasing development of e-commerce activities, where dealers often conceal their physical address.

Well, in emergency situations, unfortunately, all these risks are amplified. Human needs related to disasters impose urgent reactions, especially if they affect poor and overcrowded communities with low standards of living, which are more exposed to outbreaks of infectious disease. So, large amounts of medicines have to be rapidly collected, dispatched on the area of operations as soon as possible and, once there, immediately distributed for consumption or stored.

Any step of this complicate process may present significant problems considering that responsibilities concerning the prevention of diseases and treatment of those affected are often shared by different actors, such as ministries of health, other international agencies, non-governmental organizations and the communities themselves.

First of all, the medicines to be collected - by purchasing on the market and / or accepting gifts from both public and private entities – have to meet the needs emerging from disasters, but they have also to comply, if collected elsewhere, with the drug policy of the concerned countries.

Second, even if a formal correspondence between needs and medicines is established, there is always the possibility of substandard / spurious / falsely-labelled / falsified / counterfeit medicines depicted above.

All these risks are increased by potential lack of communication and / or misunderstanding among relief structures and health authorities of concerned countries, problems which, alas, are quite normal in areas heavily affected by conflicts/disasters.

Furthermore, bad storage and transport conditions can deteriorate medicines, provoking a decrease in their therapeutic activities. The level of risk is especially high in connection with big stocks of temperature-sensitive pharmaceutical items, such as vaccines, insulin or other biological products; in many cases, in large-scale disasters, it is difficult, for obvious reasons, to find (or to create) and maintain conditions for a proper storage of the medicines in the area of intervention.

Also considering the risk of misusing medical supplies in relief operations, **Resolution 19** of the 25th International Conference of the Red Cross and Red Crescent, held in Geneva in 1986, sets out general criteria about the use of medical supplies, including quality assurance requirements.

It is recommended that each National Society and government wishing to participate in ICRC or IFRC relief operations requiring medical relief supplies should limit their gifts to the needs identified by the ICRC or IFRC in prior consultation with those organizations. These medicaments and/or medical supplies should be in accordance with guidelines issued by the ICRC and the IFRC, under the supervision of qualified health personnel and in conformity with the recipient country's drug policy, if any.

Furthermore, the Resolution recommends that National Societies and governments participating in Red Cross and Red Crescent relief operations should use the W.H.O. Standard list of drugs and clinic equipment for IFRC operations and the ICRC Standard list of medicaments and medical material for ICRC operations.

Last, it recommends that all medicaments and medical supplies provided through the ICRC or the IFRC should be packed and labelled in accordance with the guidelines issued by the ICRC or the League, depending upon the character of the operation.

Resolution 19 has been further implemented at the IFRC level by adopting an **Essential Drugs and Medical Supplies Policy** during its 12th Session of the General Assembly in October 1999. According to such a policy, the Federation shall in particular:

- ⌚ base selection of drugs and medical supplies primarily on the national list of essential drugs; where such a list is nonexistent or incomplete, the World Health Organization list of essential drugs can be used with a focus on the basic health needs of the target population;
- ⌚ use the international non-proprietary names (generic) in drugs selection and procurement whenever feasible;
- ⌚ adopt a procurement strategy that ensures the availability of drugs of good quality, safety and efficacy at the lowest possible price without undermining the financial sustainability;
- ⌚ apply the W.H.O. Certification Scheme on the quality of pharmaceutical products moving in international commerce and other feasible methods for assessing the quality of pharmaceutical products in the process of procurement;
- ⌚ undertake all measures for organizing proper storage and a distribution system that safeguard managerial efficiency and ensure adequate quality of the pharmaceuticals at all levels;
- ⌚ request donors to observe the obligation of providing good quality essential drugs with an acceptable range of shelf-life;
- ⌚ adopt the W.H.O. guidelines for drug donation and take all possible measures to ensure their application at all levels;
- ⌚ support the rational use of essential drugs and medical supplies through the promotion of rational procurement, distribution, prescription, dispensing and consumption of pharmaceutical products at all levels; to this effect, organize and undertake educational activities for selected categories of health care workers and consumers in collaboration with national and international organizations and formulate the necessary guidelines that assist the establishment of a sound supply and management system;
- ⌚ Take appropriate measures complying with national and / or international guidelines for the timely disposal of expired and unwanted drugs.

The staff and volunteers involved in the execution of health programs have to be well oriented as to the rationale and content of this policy which is disseminated among collaborating organizations at local, regional, national and international levels.

The relevance of such issues for the work of the Movement has also led the IFRC to adhere to the **Sphere Project**, a voluntary initiative among a [wide range of humanitarian agencies](#) established in 1997 in order to improve the quality of humanitarian assistance and the accountability of humanitarian actors to their constituents, donors and affected populations.

Within this project a set of health systems standards has been defined, covering issues related to drugs and medical supplies.

Some of these standards - published as a Handbook, last revised in 2009/2010 – replicate, substantially, the criteria set out in the above mentioned Resolution 19; it is actually recommended to accept donations of medicine only if they follow internationally recognised guidelines.

Other standards are, instead, more specific and, I would say, operational provisions. It is recommended to review the existing lists of essential medicines of the disaster-affected country early in the response to determine their appropriateness. This action has to be carried out in consultation with the lead health authority early in the disaster response. If an updated list does not already exist, guidelines established by W.H.O. should be followed. The use of standard pre-packaged kits should be limited to the early phases of a disaster.

These standards also require to endorse a standardised essential medicines and medical equipment list that contains items appropriate for the health needs and the competence level of health workers. The equipment can be diversified at different healthcare levels according to the competency of the available staff; essential medicines for the treatment of common illnesses should also be available.

It is recommended as well to establish or adapt an effective medicines management system in order to ensure the efficient, cost-effective and rational use of quality medicines, storage and correct disposal of expired medicines. This system should be based on the four key elements of the medicines management cycle: selection, procurement, distribution and use.

As you can see both Resolution 19 and the Sphere Project Handbook leave room enough for carrying out quality assurance activities, but if we want to have an idea of the magnitude of such problems, I think we have to look into the following case-study concerning massive use of biological products in critical situations, including bad climate and poor logistical support.

It concerns the **Measles & Rubella Initiative**, a global partnership established among the United Nations Foundation, the Centers for Disease Control and Prevention, UNICEF, the W.H.O. and components of the Movement in order to provide technical and financial support to governments and communities on vaccination campaigns and disease surveillance.

The Initiative - which supported vaccination campaigns in more than 60 countries, mostly in Africa and Asia – is still ongoing with further goals to reach in future years.

In this framework, in particular, the IFRC keeps on directing funds to enable National Societies to participate in their countries' vaccination campaigns. National Societies and their volunteers work to maximize vaccination coverage by reaching the most vulnerable people in the most hard-to-reach and impoverished areas. This is done through community-level activities, including house-to-house visits to promote vaccination.

More than 100,000 Red Cross Red Crescent volunteers have participated in measles campaigns to date, in almost every region of the world.

THE PROBLEM:

- **in 2000**, before the Measles & Rubella Initiative formed, **more than 535,000 children worldwide died from measles each year**;
- while significant progress has been made thanks to the Initiative and its supporters, **measles still kills an estimated 139,300 each year** – mostly children less than five years of age. That means approximately 380 die from measles-related complications each day. Rubella is another disease the Initiative is now addressing.

In many developing countries, parents do not have access to immunization services that could protect their children from this fate. Factors such as poverty, poor health systems and a lack of information can make it difficult for families to secure preventative vaccinations for each of their children.

The risk also remains in developed nations. Although measles was eliminated from the Western Hemisphere in 2002 and endemic rubella has not been detected in the Americas since 2009, outbreaks can occur when unvaccinated residents are exposed to infected people, mostly through international travel.

THE SOLUTION

Since 2001, the Initiative has **supported 80 countries** to deliver **more than 1 billion doses of measles vaccine**, helped to raise measles vaccination coverage to 85 percent globally, and **reduced measles deaths by 74 percent between 2000 and 2010**. These efforts have contributed significantly to reducing child mortality as per Millennium Development Goal 4.

Initially focused on Africa where the disease burden was highest, the Initiative provides technical and financial support to governments who require support to control the spread of these diseases.

Building on its success, the Initiative now supports vaccination campaigns worldwide.

Its goal is to reduce measles deaths worldwide by 95 percent by 2015 and eliminate measles and rubella in at least five of the six World Health Organization regions by 2020.

THE STRATEGY

The Initiative's strategy relies on five components.

- Achieve and maintain high levels of population immunity by providing high vaccination coverage with two doses of measles- and rubella-containing vaccines through routine immunization and campaigns;
- Monitor disease using effective surveillance and evaluate programmatic efforts to ensure progress;
- Develop and maintain outbreak preparedness, respond rapidly to outbreaks and manage cases;
- Communicate and engage to build public confidence and demand for immunization.

- Perform the research and development needed to support cost-effective operations and improve vaccination and diagnostic tools.

Because many countries do not yet have the systems and capacity in place to reach all children with routine immunization services and poor children are more likely to be missed, the Initiative emphasizes mass vaccination campaigns as an effective strategy to ensuring nationwide coverage and reaching the un-immunized.

A measles vaccination campaign refers to the process of vaccinating all children in a defined age range in a short period of time, often just a few days or weeks. Campaigns are usually countrywide but may take place in multiple phases. On average, Measles & Rubella Initiative campaigns successfully reach more than 90 percent of the children targeted. The Ministry of Health within each country is responsible for planning and conducting the campaign with technical and financial support from the Initiative partners.

The Global Measles and Rubella Strategic Plan identifies **67 priority countries** to support, based on the level of their routine vaccination coverage for measles and status of introduction of rubella vaccine.

THE VACCINE

The Initiative helps procure the measles vaccine from pharmaceutical companies and delivers it to countries organizing measles vaccination campaigns. **The vaccine used is verified to be safe and effective by the W.H.O..**

The Initiative also works with each country to ensure that a system is in place to maintain the vaccine at the proper temperature until it reaches the children who need it.

Each vaccine can be purchased and administered for less than US \$1, making it one of the most cost-effective health interventions available.

THE IMPACT

The Initiative leaves a lasting impact on global health in different ways.

Firstly in terms of **Mortality Reduction**. As said above, with intervention by the Initiative and commitment from governments around the world, global measles deaths worldwide fell by 74 percent between 2000 and 2010, from an estimated 535,000 to 139,300.

The Eastern Mediterranean region has seen measles deaths drop by 93 percent from 2000-2008. With this sustained accomplishment, the region met the United Nations' goal to reduce measles deaths by 90 percent by 2010, three years early (2007). The significant decline in measles deaths in this region was the result of intensified vaccination campaigns including several countries with hard-to-reach areas. In 2007, health workers immunized more than twice the number of children in campaigns than the previous year.

In the African region, measles deaths decreased an estimated 85 percent between 2000 and 2010. However, a number of countries experienced outbreaks in 2008 because of gaps in immunization coverage—both with the first dose delivered through routine

immunization services as well as children missed during campaigns. The risk of resurgence of disease in Africa is great, reinforcing the importance of timely campaigns and stronger immunization services.

The progress in Southeast Asia has been limited. With a 46 percent decline in measles deaths, hundreds of children are still being infected by this disease every day. In 2008, an estimated three out of four measles deaths occurred in India – the only priority country yet to implement the comprehensive measles mortality reduction strategy. The goal of reducing measles deaths worldwide by 90 percent is dependent on the Indian government taking action. The Ministry of Health has shared plans for campaigns in 2010, and the Measles Initiative has offered both technical and financial support.

The Initiative also impacts in terms of **Surveillance Systems and the Laboratory Network**. Effective surveillance for measles actually includes investigation and laboratory testing of samples from all suspect measles cases. The Initiative builds upon the surveillance and laboratory system established by the Polio Eradication Initiative. By the end of 2010, 41 of the 47 priority countries for measles control had implemented case based surveillance with support from the Measles Initiative. Measles surveillance is integrated with other disease surveillance systems resulting in improvements in infrastructure, capacity building, and provision of needed personnel and outbreak response.

Given the overlap of the clinical presentations of measles with other fever-rash illnesses (e.g. rubella, Parvovirus B19, HHV-6 and dengue), it is critical that a laboratory investigation is carried out to confirm suspected cases as measles. Since 2000, the W.H.O. Measles and Rubella Lab Network has tripled in size from 228 to 679 national and sub-national labs serving 164 countries.

Measles and rubella surveillance is an important tool for measuring the disease burden, studying morbidity and mortality trends, and detecting and responding to outbreaks in a timely manner. It also provides essential data to monitor progress, improve planning and help allocate health resources more efficiently. Surveillance and the laboratory network play a critical role in directing program activities.

The Initiative impacts in terms of **Routine Immunization** as well. One component of the measles & rubella control and elimination strategy is to provide every child with a dose of measles and rubella vaccine by their first birthday through the routine health system.

The Initiative supports this strategy by providing technical and financial support. Global routine measles vaccination coverage reached 85 percent in 2010; a significant increase from 72 percent in 2000.

Coverage varied substantially by geographical region, with African and Southeast Asia still under 80 percent (2008). Sixty percent of the world's 19 million unvaccinated infants reside in six populous countries with India, Nigeria, China and Ethiopia, each having more than 1 million.

The world's poorest children, who are less likely to receive the vaccine through the routine health system, are at a greater risk of contracting measles and dying from complications. Without interventions by the Initiative, such as outreach and intensified campaigns, they remain vulnerable.

Lastly, the Initiative impacts in terms of **Integrated Campaigns**. Measles campaigns typically reach over 90 percent of all children targeted. This provides an opportunity to deliver other health services chosen by the Ministry of Health and based on country needs.

Between 2001 and 2010, the Measles Initiative and its partners supported the distribution of more than 41 million insecticide-treated bed nets, 213 million doses of vitamin A, 127 million doses of polio vaccine and 94 million de-worming tablets.

By offering multiple health care interventions, the Initiative increases community participation, is cost effective and addresses a variety of health problems.