Good Manufacturing Practices

How Serious is the Government

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Through a notification the government has introduced a draft amendment to the Drugs and Cosmetics Rules, 1945 which are aimed at introducing Good Manufacturing Practices (GMP) in the pharmaceutical industry. But clearly, the government is not at all serious about implementing these measures as becomes obvious if the draft GMP is scrutinised.

THE DRUGS and Cosmetics Act, 1942 and Drugs and Cosmetics Rules, 1945 are both ancient laws. They have to render minimum check and control on production, distribution and marketing of modern pharmaceuticals. It is also proved that this Act and its rules although amended in 1979, 1980 and 1982, cannot provide the government adequate power even to ban a harmful drug. The Government of India, through a notification of June 22, 1987 had introduced a draft amendment to Drugs and Cosmetics Rules, 1945. The amendments are aimed at introducing Good Manufacturing Practices (GMP) and it is stated in the notification that:

> Any objection or suggestions which may be received from any person with respect to the said draft rules before the expiry of the period (thirty days from the date on which the copies of the official gazette in which this notification is published are made available to the public) so specified will be taken into consideration by the Central government.

What is GMP

In USA in the early 70s a large pharmaceutical company was convicted when due to faulty manufacturing practices, a drug manufactured by them caused a large number of deaths. The same company, aiming to refurbish its image and goodwill proposed to other manufacturers a self regulatory code for manufacturing of pharmaceuticals. Later, the World Health Organisation took the initiative to prepare a norm of Good Manufacturing Practice. At the 28th World Health Assembly in 1975 the revised text of 'Good Practices in the Manufacture and Quality Control of Drugs' was adopted. It was recommended that all member states (which includes India) should apply the requirements of good manufacturing practice.

The practices laid down in GMP are designed to ensure that the drugs received by the consumers have been subject to stringent control from the beginning to the end of the manufacturing cycle to ensure that they are of high quality. The expression 'manufacturing' for this purpose refers to all operations involved in the production of a drug including processing, compounding, formulating, filling, packaging and labelling.

WHO has grouped GMP in mainly the following sections—personnel, premises, equipment, sanitation, starting materials, manufacturing operations, labelling and packaging, quality control system, self inspection, distribution records, complaints and report of adverse reaction. It has provided very broad guidelines of GMP for its adoption in a suitable form by the member countries. It took India about a decade to think of implementing the decision of the World Health Assembly on GMP.

Without a high standard of ethics it is impossible to maintain GMP. In developed countries drug manufacturers had, on several occasions, faced strong criticisms, litigations resulting in heavy compensation and stringent government regulations. The GMP is self-regulatory and not a compulsion under law in the developed countries. It was found that the same international company which maintains GMP at their establishments in parent countries, does not care to do so at their establishments in the underdeveloped third world countries. In some countries statutory actions have to some extent forced the multinationals to follow some kind of ethics. The Indian experience is different. The Committee on Drugs and Pharmaceuticals (Hathi) expressed its concern on the rampant violation of laws by the drug multinationals in India. Despite this, the Government of India had decided to enforce GMP only by changing the statute. It is, therefore, necessary to analyse the nature of the amendment the government intends to introduce and the consequences of the statute if it is truly implemented.

Some Problems Relating to GMP

WHO had suggested Good Manufacturing Practice for the manufacture of formulations only. There is as yet no code/guideline for manufacturing basic bulk drugs. This is particularly disturbing when now-a-days multipurpose pharma plants are capable of producing more than one drug in the same process plants.

A company may produce a combination of two or more drugs of high technical quality and bioavailability but the combination itself may be irrational and not needed by the population of the country where it is marketed. GMP should also cover these drugs. WHO had defined GMP as 'pre-marketing quality assessment' the essential factors of which are:

"A notification procedure: is the the least resource-intensive ways of obtaining information on drugs offered sale in a country. The amount of information required for notification may vary. It may be initially restricted to the name of the drug and manufacturer, and may then be expanded to include the nonproprietary names for active substances, the composition, including inactive ingredients, and pharmacological classification". This will eliminate all irrational formulations which have no place in any standard books of pharmacology.

"An authorisation procedure: can be developed in which either all drugs or specified ones only require an authorisation before they are marketed in the country. This may vary

in its stringency but it almost always incorporates the element of inspection of the manufacturer and the verification of product quality by analysis.

"A registration procedure: comprises the evaluation of data intended to prove the safety and efficacy of the drug and to determine the indication for its use. The registration may include an assessment both of the drug and of the manufacturing procedures".

Pre-marketing quality assessment therefore should form an integral part of GMP. This is missing from GMPs adopted in most of the countries.

The other thing which is missing in these GMPs adopted in the other countries is a complete set of guidelines for post manufacturing surveillance which should include the marketing code also. This we need to discuss more in the context to our country.

It took a decade for the Government of India to formulate GMP after they participated in 28th World Health Assembly where the resolution on GMP adopted. It is clear why the government suddenly became so conscious of the need to introduce an amendment and pass it in a short 30 days' time. This of course, follow the recent pattern of the government taking snap executive decisions bypassing even the Parliament. Causal, non specific and absurd rules have been suggested that too without determining any logistics for their implementation.

We have three major laws and regulations which govern production and sale of drugs: Drugs and Cosmetics Act 1942; Drugs and Cosmetics Rules 1945; Magic Remedies Act. In UK the main law is the Medicines Act, 1971. There were 34 regulations set out by British government (upto 1981) to govern the production and sale of drugs many of which are directly and indirectly connected to GMP.

There are major inadequacies in the government's draft GMP as far as the premises and equipment are concerned. In the draft only eight points are mentioned while in British GMP there are twenty-two specific directives. The draft says: "They (the building) should conform to the conditions laid down in the Factories Act, 1948 (63 of 1948)'. It is well known that because the age-old Factories Act has been of no use in regulating the conditions of the technologically developed modern factories the government has brought forth a further amendment to the Factories Act. What type of control then can one except from this Act on the 'high tech' pharmaceutical factories?

The draft also had not cared to look into the effect of factories on environment inside and outside the premises. There are international standards on the limit of toxic materials and suspended particles in the air. The draft GMP has totally ignored it. Not only this, the draft has not dealt with the disposal of containers of bulk drugs and other materials which may not loose potency by simple washing with soap water. Nor does it mentioned how and where to dispose toxic effluents. The British GMP, in contrast to our draft, says:

> Waste materials should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings, and disposed of at regular and frequent intervals. Special care is necessary over the disposal of waste containing dangerous, highly toxic or sensitising materials (eg hormones, cyto toxic agents, sensitising antibiotics). Disposal of raw materials, printed packing materials and rejected products should be carefully controlled and documented.

The draft is extremely casual in this area. It is very vague and non specific when they state that the manufacturing area for sterile drugs "shall be provided with air locks for entry and shall be essentially dust free and ventilated with an air supply through bacteria retaining filters (HEPA filters)". While British GMP has a separate chapter containing 126 sub clauses for 'Manufacture and control of Sterile Medicinal Products', our legislators had to be satisfied with only two tiny paragraphs.

Various HEPA filters are used to create sterile conditions of air for different purposes. Therefore, a standard is needed to be fixed for production area of sterile materials. Not only this, there should be standardisation of specific final filter efficacy with recommended minimum air changes per hours and the equivalent classification of HEPA filters available in India. Absence of such standardisation will lead to the controversies in application of strictures and the manufacturers will take recourse to some other laws to evade this vague stipulation.

Another classic example of casual approach can be found in the draft under the peculiar heading 'All Medical Services' that "Medical inspection of workers at the time of employment and periodic check up thereafter once in a year, with particular attention being devoted to freedom from infection conditions and records thereof shall be maintained".

It is beyond the scope of anyone's understanding as to how check up once in a year will ensure that the workers had no infection in the remaining days of the year. We are yet to imagine a worker who is suffering from infective cold voluntarily informing the management of his ailment. When there are a large number of contract labourers working in both big and small companies reporting of such minor but contaminous disease may mean loss of wages for the entire week. British GMP is somewhat more specific in this respect: "There should be preemployment medical checks, and steps should be taken to see that no person with a disease in a communicable form, or with open lesions on the exposed surface of the body, is engaged in the manufacture of medicinal products."

The staff should be required to report infections and skin lesions and a defined procedure followed when they are reported. Supervisory staff should look for the signs and symptoms of these conditions".

In the industrial policy declaration of 1984-85, the government announced broad banding in the pharmaceutical industry. Astoundingly the government under the scheme mentioned that equipment each as mass mixers, cone blenders, drying ovens can be used under broad banding. The British GMP has elaborately dealt with how to avoid cross contamination and mix-up. The draft Indian GMP has only mentioned the term mix-up in a subheading but nothing has been specified as to how to prevent it. Nothing has also been specified regarding the use of masks, gloves, etc, in different manufacturing area.

There should be certain codes for pharmaceutical machinery manufacturers also. For example in most of the hot air driers the lining used is asbestos. The inner walls of such driers, particularly for drying pastes, are usually coated with heat resistant paints. There is every possible chances that such paints may be dislodged from the inner surface and get mixed up with the paste or powders kept in the trays.

It is also necessary that the GMP defines clearly the maximum permissible operations per punches of the tablet compressors after which they should be discarded. Similarly it specifies limits per use of filter bags of the fluidised bed driers, etc.

Experts who had drafted the GMP are so confident of their work that they feel that their work will remain unaltered for eternity. The draft has not suggested a periodical review of the conditions recommended. The first edition of 'Guide to Good Pharmaceutical Manufacturing Practices' was published in UK in 1971. Thereafter it was amended in 1977, and in 1985. It clearly states—"Time has shown that it would be helpful to rearrange and in places, clarify and enlarge the text and to give on further topics." Due to advancement in technology and scientific concepts GMP cannot remain static. In future GMP will need to include norms for electronic data processing and retrival systems.

Quality Control Laboratory

The section on laboratory practice is the most important and sensitive part of GMP. In fact a separate set of law/guideline is needed for this. In the 28th World Health Assembly it was decided that a comprehensive review of approaches to quality assurance system would be made (WHA 28.66). A document accordingly was prepared by the Experts Committee and its report was published in the twenty-seventh report of the committee. Thereafter, the committee has produced three more reports elaborating the quality assurance systems. The thirtieth report had reviewed and added more recommendations to the earlier reports. The draft Indian GMP has ignored these facts. In the 28th World Health Assembly a small guideline was prepared on quality control system giving some objectives. The draft GMP has simply reproduced these guidelines but has not elaborated on either the methodology or the stipulations which are needed for good laboratory practice.

A major decision which is needed to be taken is whether there should be any commercial establishments for certifying quality assurance. After the facts revealed in Justice Lentin's Commission chart how political power and profit dictates the reports of the private laboratories, it is high time we decided whether any private commercial laboratories be allowed to test drugs. On the other hand the government has only five test laboratories in the country to cater to 9000 drug firms registered under DGTD.

Further the government has not considered the prevailing set up in India while preparing a new edition of the Indian Pharmacopea which is a 90 per cent replica of the British Pharmacopea. Any unit, big or small wanting to establish its own quality control laboratory will definitely need microbiology testing system spectrophotometry system for both ultraviolet and visual range, etc. While the former needs a large of space and special furniture the latter costs a large amount of money. The minimum necessary equipment for such a laboratory needs an investment of Rs 3 lakh. The definition of a small scale industry till date is a company having turn over of Rs 50 lakh. How can such a company invest Rs 3 lakh for a quality control laboratory?

Moreover, considering that all companies would have their own quality control system where maintainence of a spectrophotometer would be a must would our government laboratories be in a position to supply International Chemical Reference Substances of all drugs (both active and inactive substances) for regular calibration of their instruments. Our experience is that even the government laboratories do not maintain all reference substances to calibrate their own spectrophotometers. The draft amendment only says: "Every manufacturing establishments shall have a quality control department supervised by approved expert staff. . ." It does not say anywhere what should be the minimum equipment to be maintained in this section.

It is also necessary to clearly describe the premises of the quality control laboratory—how they should be arranged; what are the hygenie conditions, temperature, humidity, sterility conditions etc to be maintained inside. How the instruments are to be calibrated and how often their sensitivity be checked under what standard. Similarly, the reagents need to confirm to a standard guideline. Guidelines for maintaining concentration, standardisation factors, shelf life and storage factors, should also be specified and how often the prepared reagents should be checked to find out their suitability, etc.

There should be clear guidelines as to the stage of collection of samples for quality testing and for identifying, preserving and recording the samples before and after testing. Documentation of the analysis is also of great importance as well as a good documentation system.

The draft GMP had not considered many other substances which are used for curative purposes. No GMP had been suggested for the manufacture of medical gases, or of radio pharmaceuticals. A large number of verterinary medicines are also used in ur country. The draft GMP says nothing about these not even that the GMP for other pharmaceuticals should be followed in producing veterinary medicines as well. Interestingly the British GMP says: "Some veterinary products such as those used for mass external treatment of animals (e g, sheep dips), have no direct equivalent among products for human use and the recommendations on manufacturing premises and equipment given elsewhere in the guide may not be appropriate."

Post manufacturing GMP

Two most important points not given any consideration at all by the draft GMP are post marketing surveillance and distribution. The responsibility of a drug company does not end with the manufacturing of a drug. The manufacturer needs to take care that the drug is stored under prescribed appropriate storing conditions in the factory warehouse and the same has to be followed by the middle men engaged in wholesale and by the retailers in the chemist shop also. Clear guidelines are needed to be specified for transport conditions particularly for a vast country like India. Where products in transit may be subject to conditions such as unacceptable degrees of heat, cold, light, moisture or other adverse influence including attack by micro-organisms and pests.

There should be certain specified norms regarding maintenance of stocks which are rejected due to damages for spillage or breakage. These are to be kept separated from the stocks of expired drugs. Proper recording, labelling and disposal is also to be specified. Therefore GMP should include 'Good pharmaceutical storage, distribution and/or wholesale practice' also.

There is virtually no system in our country to supply package inserts along with each sales pack of drugs giving important side effects, precautions, adverse reactions, interaction with other drugs, etc. Lack of proper norms of labelling has led to situations where sometimes it is very difficult to decipher the constituents of the active ingredients of the drugs from the labels. Brand names are printed in bold while the generics are printed in or in very small type.

In 1968, the 21st World Health Assembly adopted a resolution (WHA 21.41) urging member countries to enforce control on advertisements. The resolution stated the ethical and scientific criteria for pharmaceutical advertising and covered advertising to the medical and related profession as well as to the public. From the perspective of consumer protection, it is important that the consumer should be alerted to all side effects, contraindications, warnings, hazards, and precautions. It has been observed that a fair balance can be considered to be lacking if:

a) Information is included in an advertisement that has not been approved for inclusion in the promotional material at the time of registration.
b) Advantages are claimed for the drug without simultaneous disclosure of disadvantage.
c) Obsolete information is used.
d) Claims are exaggerated.
e) Animal or laboratory data are cited as clinical experience.
f) A statement by a recognised authority is quoted without also citing any unfavourable opinions of that authority.
g) Statements are used out of context.
h) Statistics are used in a misleading way.
i) A headline or pictorial presentation is misleading (*Guidelines for the Development of a National Drug Control Programme*; Pan American Health Organisation; pp 79-80)

The draft GMP shall include all these conditions for the dissemination of correct and unbiased information.

Monitoring of a drug, new or old is continuous work. It has international impact also. Since 1960, the World Health Organisation had been insisting that all member countries should develop centres for monitoring adverse drug reactions. In the 1963 World Health Assembly it was resolved that the member countries would co-operate with each other in the dissemination of adverse drug reaction so that the best possible protection can be offerred to consumers.

In our country, no system of monitoring adverse drug reactions had been set up. Although a few such centres are in existence but they are often found to defend the hazardous drugs instead of monitoring their adverse reaction. A centre under the University College of Medicine, Calcutta was found, a few years ago, to be conducting a study financed by an industry house on the need of a combination drug—chloramphenicol and streptomycin. The head of the centre later published their study in support of this irrational and hazardous combination in the *Journal of Indian Medical Association*.

The draft GMP, under the subhead 'Records of Complaints and Adverse Reaction' only says that—"Reports of serious adverse reactions resulting from the use of drug along with comments shall be informed to the concerned licensing authority". This is the only thinking expressed in the draft regarding adverse drug reaction. The total responsibility has been left to the manufacturers who have no mechanism to keep track of adverse drug reactions. Their tendency is to suppress such information however rare it may be. Even accepting the fact that a manufacturer may report some incidents of adverse drug reaction, what would the government do? The draft GMP suggests nothing. In the event of such incidents, the British GMP elaborates on how to recall the product. The system of recall inflicts a red alert. It not only stop the sale of the product but also directs stoppage of the production operation till the reasons for adverse reaction are explored after investigation by the government authorities.

From the above, it can be concluded that while preparing the draft GMP, the government had not been in the least serious. Incomplete measures, casualness and pro-manufacturers bias to more or less maintain existing frivolous attitude to the safety of the consumers has been reflected in the clauses of this draft. Moreover it will be impossible for the small scale industries to follow this GMP, if the ammendment is converted to law. It will be impossible for them to establish full fledged in-house quality control laboratories. It will also be impossible for the old industries particularly those which are situated in the densely populated area or housed inside old industrial estates to expand the manufacturing area as required by the GMP. Therefore, the incoming GMP will have to compromise with the industry irrespective of their size and capability in the areas of quality of products and will in no way bring minimum safety and security to the consumers and workers of the pharmaceutical industry.

A Note

THIS note is to inform the readers of *RJH* that from June, 1988. I shall be moving from the category of Working Editors of RJH to that of the Editorial Collective. The reason for this shift is that for the past one year I have moved out of Bombay to a small village in Pune district of Maharashtra for a period of five to six years. I have thus hardly been a 'working' editor during this period.

It is only due to my persistent request that the other Working Editors have finally, and reluctantly, agreed to let me shift out. Moving out creates in me a feeling of deep personal loss because all the three Working Editors, as well as some of the comrades in the Editorial Collective of *RJH* are my closest friends. During the next five years I shall greatly miss the warmth and the intellectual stimulation that the RJH collective has always offered to me.

I shall certainly continue to stay within the Editorial Collective of *RJH* because I fully believe in the ideological perspective of the Journal and have no differences either political or personal with the form and content of RJH. I am sorry that I am not able to undertake more responsibility on behalf of *RJH*, much as I want to. And, I am aware that the loss is mine.

In solidarity

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