REPORT OF THE 49TH MEETING OF THE DRUGS CONSULTATIVE COMMITTEE HELD ON 16TH OCTOBER, 2015 AT NEW DELHI

INAUGURAL DELIBERATIONS

1. Dr. G. N. Singh, Drugs Controller General (India) and Chairman, Drugs Consultative Committee, welcomed the participants to the meeting. He apprised the Committee that Shri K. L. Sharma, Joint Secretary, Ministry of Health and Family Welfare is amongst us today to share his views on a variety concerning regulation of medical products in the country.

2. Dr. G.N. Singh briefed the members that the meeting has specifically been convened to discuss issues relating to strengthening of Drug Regulatory System in the country, evolve a strategy to check misuse of oxytocin on milch cattle and the steps required for upgradation of the GMP to WHO level.

3. He also mentioned that Central and State drug regulators should utilize the resources allocated in 12th Five Year Plan judiciously so that there may not have any scope for duplication of regulatory works among themselves except wherein there is technical need for doing it in larger public interest explaining scientific justification behind it.

4. Dr. Singh also informed the members that Smt. Maneka Sanjay Gandhi, Hon'ble Minister of Women and Child Development would also be interacting with the Committee members on issues concerning oxytocin at 1500 hrs. He requested Shri K. L. Sharma to share his thoughts with the members.

5. Shri K. L. Sharma thanked the Committee for having invited him for this meeting and recollected that when he interacted with the Committee a year back, an agenda had been set out to substantially upgrade the drug regulatory structure in the country and everyone present in that meeting had agreed that it would be the endeavor of each of the participants to work towards achieving excellence across the country. He added that it has been a matter of satisfaction that there has been some change in the perception over a period of one year but the pace has been rather slow and we need to put in a little more effort especially in the context of the commitment of the union Government to strengthen the system and make it more effective and transparent as exhibited by the approval of the proposal for strengthening the regulatory structures in the centre and in the States and the UTs. He added that the aim would be to make the Indian drug regulatory system a benchmark for others to follow and emulate through close coordination between the Centre and the States. He stressed that the uniformity of approach and action between the States and Central Drug Control structures would be necessary for this to happen.

6. Shri Sharma stated that the Central Government has initiated a new capacity building programme for modernizing and strengthening of the Drug Regulatory System in the country. For this purpose an amount of Rs. 900 crores has been sanctioned for strengthening CDSCO. A plan to utilize the funds for the CDSCO has already been put in place.

7. He added that an outlay of Rs. 850 crores has been sanctioned for the States for strengthening the infrastructure as well as testing capacity. The amount is required to be spent over 2015-16 to 2017-18. The States have been apprised of the indicative amounts likely to be made available to them and have repeatedly been requested to submit their schemes and sign the MoU. However, only a few States have responded so far. He added that this afforded a golden opportunity to make the much needed difference and it would be

painful if the opportunity is not encashed by the individual State Govt. regulatory system. As part of the scheme, the present drug testing laboratories are to be strengthened and new labs, wherever required, established. He added that in about two years' time, every drug testing lab has to be necessarily accredited with NABL and the non-accredited labs will not be allowed to do drug testing. He also informed that the CDSCO is already organizing training programmes for educating the lab personnel about NABL accreditation process and a nodal group would also help individual labs to seek clarification about any process related issues. He also clarified that programmes for ISO certification are also being organized and each drug regulatory office should be ISO certified.

8. He also emphasized the need for early adoption of e-Governance. It was emphasized that in order to bring more uniformity in the processes across the country, a number of training programmes are on the anvil and a few such programmes have already been initiated. The programmes for 40 Drug Analysts from all over the country from central and State labs was very well received. Yoga has been made an integral part of the training programmes.

9. Joint Secretary, MoHFW underlined the fact that an efficient drug regulatory system in the country can only help in realizing the potential of the country in pharma sector and pave the way for making the country a major player in other medical products. He stated that inadequacy of the structures can be gauged from the fact that regulators of importing countries point out deficiencies in our manufacturing units and magnify them and thereby impact export from the country. He underlined that the present level of export could increase many fold if the quality related issues could be conclusively addressed. He added that regulatory incapacity cannot be allowed to stand in the way of realizing the potential of the country. He elaborated that the image of India as the 'Pharmacy of the world' gets impacted even if a few substandard drugs get

manufactured or Good Manufacturing Practices are not followed in letter and spirit and the regulatory structures do not ensure their enforcement.

10. The manufacture of medical devices in the country is another area where India can take a lead by leveraging the demographic dividend and comparative cost advantage. As part of the Make in India, such manufacture is planned to be taken up by the Government in a big way. The Central Government is planning to set up medical devices testing laboratories and these will be set up in the States on the basis of the infrastructure and the quantum of manufacture of medical devices in that State and also whether the State is able to provide land for the purpose free of cost.

11. Shri Sharma also pointed out those cosmetics is another sector where India has a huge potential. The sector offers immense potential for employment generation and wealth creation. India has the potential to become the hub in this sector to cater to foreign markets.

12. It was highlighted that effective coordination and communication coupled with the uniformity of approach is the essence of efficient administration. Communications from the Central Government or DCG(I) and vice-versa need prompt action and response for this.

13. For enhancing transparency, the details of the licences issued by the States should be available on websites and also on CDSCO website. States need to ensure that licenses for manufacture of drugs are not issued in violation of the Drugs and Cosmetics Rules, 1945 especially in the case of FDCs. Despite clarity of position with regard to FDCs, States continue to issue licences for FDCs. Licences have also been issued in many cases where GMP requirements are not fully met.

14. He further suggested that there should be more frequent meetings either at the National and regional levels for better coordination. He also added that International agencies sometimes visit States for inspections or interactions. The States must promptly share information about any such visits or interactions by WHO, FDA, USA or such other agencies with the Central Government.

15. He also mentioned that legal action must not be initiated on the basis of drugs samples found substandard/spurious during the course of the National Survey to assess the extent of spurious/substandard drugs in the country and fresh samples as per procedures prescribed in the Act should be drawn. He also highlighted the fact that as per reports received by the Central Government, oxytocin or even concoctions thereof are being manufactured clandestinely and misused in violation of the provisions of the Drugs and Cosmetics Rules, 1945. That such violations do take place, is a reflection on the efficacy of the drug regulatory system. He exhorted all concerned to take stringent measures to eliminate such malpractices and referred to the recent steps taken by the Central Government.

16. It was pointed out that the Central Government is establishing an Academy for training of Drug Regulatory Officials, both from enforcement and laboratory set up. Suggestions had been invited from States about the type of courses required for development of human resources so that a need based curriculum could be adopted. The States should respond quickly. It was informed that as part of training programme, the Indian Pharmacopoeia Commission is also providing training to Government analysts. Eventually, it will be made mandatory for all labs to have duly qualified personnel and all Government Drug Testing Laboratories of the States should avail such opportunities so that the analysts are fully aware of the latest techniques.

17. In the context of controversy relating to sale of drugs through internet, Joint Secretary, MoHFW highlighted that we need to take a conscious view in the matter after careful consideration of the matter.

18. It was agreed that all these points will be reviewed in the meetings to be held at the regional and national level.

19. Smt. Maneka Sanjay Gandhi, Hon'ble Minister for Women and Child Development, took some time off from her busy schedule to address the DCC members. She stated that the misuse of oxytocin for milking the cows and buffalos is one of the major issues affecting public health. She emphasized that it is impacting not only the quality of milk being produced but also has adverse effect on the bovine population of the country.

20. Cows are milked by using oxytocin injection and the calves are weaned away and butchered. She added that the cows become barren over a period of three to four years because of continuous use of oxytocin injections two to three times a day. The cows have to suffer labour pains every time they are injected affecting the tenacity of uterus.

21. The consequence of this is that the livestock numbers are slowly dwindling. The whole process plays havoc with the environmental balance. Further, extensive use of oxytocin leads to development of ketosis in bovines resulting in bovine leucosis and bovine leukemia. The milk from such cows will have adverse effect on users especially children, the most prominent users of animal milk.

22. Even though oxytocin is well regulated under the provisions of the Drugs and Cosmetics Rules, 1945, it is being illegally manufactured and clandestinely

sold to the dairy owners. She highlighted that the bulk drug in the country is being manufactured by only one manufacturer i.e. Hemmo pharma, Mumbai but the formulations are manufactured by large number of manufacturers with or without valid licence. Because of large demand in the country, the bulk drug is also imported clandestinely into the country.

23. Oxytocin is also being imported clandestinely from China and a company under the name of Xio Qiang Changzhou, China is sending it as Custom Peptide to many individuals. As the product is not considered a drug, no license/permission is required for its import. It is supplied through courier agencies such as Fedex.

24. The drug is smuggled into the country at a much cheaper rate and is then filled crudely in plastic bottles which may or may not have labels. The labels even, if these are there, are fake labels. The major areas where such materials enter into India are Bihar and West Bengal across the borders. Reports are there that other channels are also used for smuggling of bulk oxytocin into the country.

25. The Hon Minister asked the regulatory authorities that this clandestine manufacture and sale can only be curbed by continuous surveillance and raids at the hideouts and sales outlets from where it is sold clandestinely. Repeated raids can only act as deterrent to stop this activity.

26. Consideration of regular agenda items

AGENDA NO. 1

(a) **Confirmation of the minutes of the 48th meeting of DCC held on 24th July, 2015**

The minutes were confirmed

(b) **Approval of Action Taken Report**

(i) During discussions on Action Taken Report in respect of constitution of the Sub-Committee to examine the issue of sale of drugs on internet, the Chairman requested the members to share whatever information or suggestion they have now or forward the same to the Commissioner, FDA, Maharashtra or Dr. S.E. Reddy, JDC(I), CDSCO(HQ), New Delhi for their consideration. He also mentioned that the Committee may submit its report at the earliest after wider consultation among the stakeholders.

(ii) In respect of training of Govt. Analysts and other regulatory personnel at Indian Pharmacopeia Commission, it was stated that the experience gained during training must be shared with other colleagues to improve quality and quantity of output at bench level performance.

(iii) It was indicated that candidate materials from the reputed manufactures in the State may be taken for use in State Drug Testing Laboratories for testing and standardization after following the procedures laid down for making working standards by the Indian Pharmacopoeia Commission, Ghaziabad (www.ipc.gov.in) The Labs should keep sufficient quantity of working standards as per their specific needs.

AGENDA NO. 2

STRENGTHENING OF DRUG REGULATORY SYSTEMS IN THE COUNTRY UNDER THE CENTRALLY SPONSORED SCHEME AND PROVIDING TRAINING TO THE STATE DRUGS REGULATORS

(i) The Government of India has agreed upon to have a capacity building programme for strengthening of drug regulatory system at the Centre and State Level. Under this scheme planned interventions are proposed in respect of a large number of activities, the details of which have already been shared with the States.

(ii) Strengthening of State Drug Regulatory System is at the cost of Rs 850 crore (excluding state share). The component of expenditure will be on cost-sharing basis between the Central and State Government. The sharing pattern between Centre and State will be 90:10 for the States of Jammu and Kashmir, Himachal Pradesh, Uttarakhand, Sikkim, and seven North-Eastern States and 75:25 for all other States.

(iii) The issue had earlier been discussed in the 47th meeting of the DCC also and it was impressed upon the members that it is high time to make optimum use of the approved plan outlay by the States/UTs both in terms of infrastructure and manpower. It was reiterated that the Memorandum of Understanding ae required to be signed quickly and other specific details need to be furnished immediately by all States/UTs.

(iv) All the members agreed to work out individually and collectively to ensure most optimal use of the resources. The Committee recommended that the Government of India may consider the continuations of the scheme for two more years beyond the approved period and provide additional resources for strengthening the regulatory system during that period. The States were of the view that the proposal of mobile vans for testing drugs was very useful for checking clandestine activities.

(v) Dr. Koshia of Gujarat stated that I.R. Spectra is good for detection of single drugs. The presence of such unit in the regulatory set up will be a big deterrent to antisocial elements. It will provide qualitative information about the presence of active drug in the sample and will be useful in checking clandestine activities.

(vi) It was agreed that for effective coordination, States should have intelligence cells. Alerts could be put on websites for information of the public.

AGENDA NO. 3

MISUSE OF OXYTOCIN

(i) The issue of continued misuse of oxytocin injection has been considered by the DCC as well as DTAB in its various meetings. It was observed that the problem has a lot to do with stricter control over the manufacture and sale of the drug especially through clandestine channels rather than sale through licenced outlets.

(ii) It was noted that in the 70th meeting of DTAB held on 18.08.2015, it was opined that the oxytocin injection manufactured in accordance with the provisions of the Drugs and Cosmetics Rules, 1945 has high costs and can, therefore not be used for extracting milk from cows. The raw material or the bulk drug for such use might be clandestinely smuggled into the country and crudely manufactured for sale to dairy owners at cheap rates.

(iii) The State Licensing Authorities were earlier requested to take a serious note of the illicit use of oxytocin injection by dairy owners to extract milk from milch animals leading to its harmful effect on humans as well as livestock and take stringent measures to check the illegal movement of the oxytocin. Raids should be conducted in suspected areas in cooperation with police authorities to apprehend anti-social elements.

(iv) CDSCO North zone, Ghaziabad had made concerted efforts and has been successful in carrying successful raids to apprehend culprits selling oxytocin injection clandestinely in Delhi.

(v) On 14.04.2015 a raid was conducted at Ghazipur dairy after due surveillance of the area along with the officers of Delhi Drug Control and Police Authorities. Large quantities of oxytocin injection in plastic bottles and other veterinary drugs were seized from their premises.

(vi) Recently another raid had been conducted on 22.09.2015 by officers of CDSCO, North Zone along with the officers of Delhi Drug Control with the assistance of the Delhi Police at New Delhi Railway Station. During the raid, huge stocks of oxytocin consisting of 3,60,000 ampoules of 2 ml each which included labeled and unlabeled ampoules along with 4440 unlabelled bottles of 100 ml each of oxytocin were seized. FIR has been filed under the Drugs and Cosmetics Act, 1940 in the concerned police station.

(vii) Further investigations have also been conducted at Gaya by the officers of North Zone and there also large quantities of oxytocin were also seized during the raid at one of the premises with the active cooperation of the District administration, State Drug Regulatory and Police authorities.

(viii) The issue has been deliberated at very high levels in the Government of India and it has been decided to investigate the source of raw material being used in the manufacture of illegal oxytocin injections sold at a very cheap rates and to find out whether crude oxytocin raw material is illegally imported into India for its clandestine manufacture and sale in the country. It has been decided to find out complete traceability in the form of oxytocin crude, its precursor or any other form which may disguise identity of the drug in violation of the Drugs and Cosmetics Act, 1940.

(ix) States have also been asked to provide information in respect of licences issued for manufacture of bulk oxytocin, oxytocin formulation, oxytocin injection to obtain a comprehensive overview of manufacture of the oxytocin in the country.

(x) DCC was in the above light requested to deliberate and give its recommendations as to how the misuse of oxytocin by dairy owners could be curbed.

Discussions and Recommendations

(i) During deliberations, it was noticed that Telengana, Delhi, Rajasthan, Gujarat and Andhra Pradesh have been able to seize stocks of clandestinely manufactured oxytocin in their States. The investigations revealed that major places from where clandestine manufacture has been reported are Gaya and Barauni in Bihar and 26 Parganas in West Bengal. The bulk drug illegally enters into India via West Bengal from the porous borders of Bangladesh through boats or other such illegal channels.

(ii) The States must provide information in respect of manufacturers of oxytocin formulations licenced in their State to the DCG (I) office at the earliest so that concerted efforts are made to monitor the manufacture and sale of the drug in the country.

(iii) Director, Central Drugs Laboratory, Kolkata was requested to develop rapid test for detection of oxytocin as the drug is filled in unlabeled plastic bottles and transported through rail or other ordinary mode of transport. For this purpose, the services of the scientists or Universities could be undertaken. This will help in detection of clandestine consignments, which otherwise do not come under the ambit of the Drugs & Cosmetics Act.

(iv) States however, lamented that even though investigations are done by the drug regulatory officials, police do not actively cooperate and is reluctant in registering FIR or apprehending the culprits. The investigations in respect of channels of supply come to dead end. The Central Govt. may instruct the State Police Deptt. to take due notice of offences relating to misuse of oxytocin.

(v) It was also suggested that FSSAI which controls production of milk may be asked to find ways and means to make use of oxytocin for production of milk as an offence under their Act as milk is regulated under the FSSAI Act.

(vi) In nutshell, following recommendations were made to fight the misuse of oxytocin in the country:

- State Drug Regulatory officials must conduct raids with the assistance of Police Authorities at the suspected outlets of such drugs near the dairy farms after due surveillance to apprehend culprits red handed.

- The manufacture and sale of oxytocin formulations by the licenced manufacturers in the State should be monitored regularly.

- States should share information about the raids conducted and results of investigations with other concerned State Drug Control Authorities and Zonal offices for interstate coordination.

- Samples of milk may be drawn to assess the presence of oxytocin in milk.

- Rapid test for detection of oxytocin may be developed.

- The Port offices of CDSCO shall inform custom authorities that import of all peptide formulations be monitored for their use.

- The Central Government may request Police authorities of States to take cognizance of offences related to misuse of oxytocin.

- FSSAI may be asked to explore the possibility of declaring the use of oxytocin on animals for production of milk as an offence under the FSSAI Act.

- Each State and Central regulatory system must develop an intelligence wing for keeping close watch, sharing of information and prompt action for checking/eradicating the misuse of Oxytocin in the country.

AGENDA NO. 4

REVISITING GOOD MANUFACTURING PRACTICES PRESCRIBED UNDER SCHEDULE 'M' IN VIEW OF WHO GUIDELINES ON GOOD MANUFACTURING PRACTICES

The following facts were brought out:

(i) The Drugs and Cosmetics Rules, 1945 under Schedule M thereof detail Good Manufacturing Practice (GMP) and requirements of premises, plant and equipment for pharmaceutical products. The Schedule was last amended vide G.S.R. 894(E) on 11.12.2001. It however, came into operation for existing manufacturers from 30.06.2005.

(ii) Good Manufacturing Practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product. GMP covers all aspects of production; from the starting materials, premises and equipment to the training and personal hygiene of staff. Detailed, written procedures are essential for each process that could affect the quality of the finished product.

(iii) WHO has established detailed guidelines for Good Manufacturing Practices. Many countries have formulated their own requirements for GMP based on WHO GMP.

(iv) In order to harmonize the provisions of Schedule M with the WHO GMP, necessary changes would be required to be made under Schedule M. CDSCO has prepared a gap analysis of the provisions of Good Manufacturing Practices and the WHO Good Manufacturing Practices.

(v) The amendment of Schedule M to harmonize it with WHO GMPs is required to be examined in consultation with State Drug Regulatory Authorities, Industry

and other stakeholders for preparations of specific draft changes that could be incorporated under the Drugs and Cosmetics Rules, 1945. DCC was requested to deliberate and make its recommendations.

Recommendation

After deliberations, it was agreed that State Drugs Controllers will forward their suggestions to the DCG (I) in the light of their regulatory experience for taking into consideration.

AGENDA NO. 5

GUIDELINES FOR UNIFORM RISK BASED AUDIT INSPECTION OF THE DRUG MANUFACTURING UNITS

It was informed that:

(i) The proposal for thorough inspection of the drug manufacturing units to ensure compliance with good manufacturing practices and good laboratory practices as prescribed under the Drugs and Cosmetics Rules, 1945 was earlier considered in the 47th meeting of the DCC held on 30-31 July, 2014. In order to ensure uniformity it was agree that the focus of inspection shall be specially on the product quality i.e. on establishing shelf life, stability studies, validation studies and ensuring prompt and effective recall as required under clause 16.10, 26.4, 27.1A of schedule M. These points need to be properly verified and reported.

(ii) The inspections of medicines and biologicals should be conducted using risk-based approach and should specifically focus on product development, stability study conducted to establish shelf life in Indian climatic conditions, process validation, complaint/recalls, handling of out of specification, deviations and change control procedures.

(iii) Certain guidelines were agreed upon which were required to be kept in mind by the inspecting teams while conducting the inspection.

(iv) DCC may consider evolving detailed guidelines for uniform risk based audit inspection of the drug manufacturing units so as to ensure that the drugs manufactured in the country conform to the required standards to ensure quality, purity, strength and consistency of drugs manufactured by them.

Recommendations

(i) The DCC, after detailed deliberations, concluded that international agencies have observed that GMP inspections in the country are of varying standards, not only at State to State level but also within CDSCO. Such perception does not bode well for the system and it needs to be fixed. It recommended that Drug Inspectors and other regulatory staff are required to be trained in the procedures of inspections so that quality of drugs manufactured in the country is uniformly maintained. Other countries especially groups such as BRICS are working hard to outclass India in export of pharma products.

(ii) The CDSCO is conducting training programmes on Good Manufacturing Practices in the country on 19-20 November, 2015 at Bangaluru. The speakers will include speakers from USFDA. States must avail this opportunity and depute at the earliest the regulatory officials for training. State should nominate at least 2 and maximum 15 officials for the programme.

(iii) WHO is proposing a regulatory Pharmacovigilance centre in India. This will be a great leap forward and will help in capturing the adverse drug reaction data in the country for further analysis and patient safety.

(iv) The CDSCO has prepared a document on standard operating procedures for conducting inspection of manufacturing premises and this was earlier forwarded to the States.

(v) States must ensure that the inspections are done in a uniform manner and in accordance to the SOPs provided so that uniformity could be maintained.

After detailed deliberations on various aspects, the meeting ended with the resolve to work together to improve the structures in the least possible time-frame and vote of thanks to and from the Chair.

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