ASSOCIATION OF REGULATORY AFFAIRS PROFESSIONALS

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Ref-ARAP-HPMC (G)/2017

15th September, 2017

To,
Dr V G Somani, JDC (I)
(Member Secretary, Expert committee) CDSCO, DGHS
Ministry of Health and Family Welfare Government of India
FDA Bhawan, New Delhi-110002

Sub: **Replacement of gelatin capsules with cellulose based capsules for encapsulation of drugs reg.**
Reference: File No. 4-01/2013-DC (Misc. 45); dated 05 Sep 2017

Dear Sir,

We would like to take this opportunity to introduce our association, the **Association of Regulatory Affairs Professionals** (ARAP), which is India's first non-profit registered society for the Regulatory affairs professionals with an objective to promote the science, pharmacy, healthcare and research in all facets and impart recent updates, education and training to regulatory affairs professionals working in pharmaceutical, medical devices, cosmetics and foods industry. Our association is representing regulatory affairs professionals from pharmaceutical, medical devices, cosmetics and foods industry nationally. ARAP has been also listed as organizational member of **Quality Council of India**, Govt. of India.

On behalf of Association of Regulatory Affairs Professionals (ARAP), we would like to appreciate the efforts and initiatives taken by your Directorate to evaluate the technical issues pertaining to the replacement of Gelatin capsules with cellulose based capsules for encapsulation of drugs. Based the factual situation, ARAP has also evaluated the issues and challenges in subject matter considering technical & regulatory aspects, and eventually its impact on Pharma Industry and India Population.
In the manufacture of pharmaceuticals, encapsulation refers to a range of techniques used to enclose medicines in a relatively stable shell known as a capsule, allowing them to, for example be taken orally or be used as suppositories.

Gelatin capsules have certain advantages over cellulose (HPMC) capsules:
Gelatin is a natural and safe product with Generally Recognized as Safe in pharmaceutical and food applications by and other Food and Drug Authorities as well as different Pharmacopoeias. Gelatin capsules are being used world over for the past 160 years without any health issues being reported by the virtue of capsule shell. Gelatin as described in the Indian Pharmacopeia (IP 2014) is a purified protein obtained by partial hydrolysis of animal collagen and is translucent, colorless, brittle (when dry) and flavorless. At present only 0.2 billion units of HPMC capsules are being used for the manufacturing of Nutraceuticals in the country, whereas 100 billion gelatin capsules are used for encapsulation of various drug formulations and as per available information in the public domain, no pharmaceuticals drug formulation in the country is being manufactured using HPMC capsules; however, gelatin capsules manufacturing technology is an old age technology, standardized over the period of the last century and has presence all across the world, with standard specification, defined by all approving authorities.

Address: 313/87,2nd FLOOR, STREET No.-3, TULSI NAGAR, INDERLOK, NEW DELHI -110035
Ph.: 011-23120260 www.arap.co.in

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Further, at present, the HPMC capsules are marketed in India by very few companies namely, M/s Associated capsules, M/s Fortcaps Healthcare Ltd., M/s Healthcaps India Ltd as India based company and M/s Capsugel, an America based company, who cannot meet the current requirements in the country. Further, the cost required for the cellulose raw material is approximately four times that of Gelatin and the manufacturing cost is approximately three times the cost of Gelatin, considering the outputs from the current available technology. As the cost for cellulose based capsule is high, its acceptance by the Pharmaceutical industry will be challenging especially in light of the drug price controls being implemented by the Govt. of India under Drugs Price Control Order. Cellulose based capsule technology is very high and there are many complexities involved like differences has been reported in properties and performance of these capsules. For example, moisture content in Hard Gelatin Capsules and non-gelatin capsules is 13-15% and 4-6% respectively; gelatin capsules can undergo cross linking during shelf life; and disintegration of HPMC capsules is affected by potassium ions; HPMC capsules show slower disintegration in acidic medium. Further, the investments required to be made for manufacturing cellulose based capsules are also substantial and will require long planning and time which may also impact accessibility of medicines to patients.

Comparison of capsules characteristic*

Property	Gelatin	HPMC
Water content	4-6%	13-15%
Gloss	Yes	Yes
Water vapour permeability	Low	Low
Oxygen permeability	Vary Low	Low
Maillard reaction with filed substances	No	Yes
Light degradation	No	Yes
Protease degradation	No	Yes
Static electricity	Weak	Strong
Solubility in water at room temperature	Soluble	Insoluble
Filling of macrogol 400 & tween 80	Possible	Impossible

Following technical aspects need to be considered while making final recommendation:

1. Gelatin capsules are used for encapsulation of various oncology medicines as well as essential drugs and therefore discontinuation of gelatin capsules will be against the public interest.
2. Cellulose cannot be used in the manufacture of soft cellulose because of their inherent properties and if the gelatin capsule is stopped in the country, raw materials for cellulose capsules will have to be imported which is against the 'Make in India' policy.
3. Cellulose is an insoluble fiber and human body does not have enzymes to digest and will lead to side effects such as blotting, diarrhea etc.
4. Cellulose based capsules containing drugs has to be used very cautiously in patients suffering from digestive tract diseases like typhoid, Chrone's disease, ulcerative colitis etc.

5. Feasibility as well as acceptability of using HPMC capsules has to be ascertained by conducting pharmacodynamics, pharmacokinetic, stability studies etc. especially with drugs which are potent and have narrow therapeutic index.
6. If the drug is encapsulated in Cellulose based or HPMC Capsules, Pharmacodynamics and Pharmacokinetics properties of the drug has to be tested before it is put in to the market.
7. Replacing gelatin based capsules with cellulose based capsules in Pharma industry would require major reviews of existing formulations including fresh stability studies to demonstrate the compliance requirement
8. Gelatin capsule have higher self-life as compared to cellulose capsules

Opinion of different statutory body:

- DTAB in its meeting held on 13.05.2016 has already opined that unlike food, drugs are not taken by choice but are prescribed by the doctor to save lives and marking them vegetarian or non-vegetarian origin is not desirable. HPMC capsule are basically of synthetically origin and as such cannot be considered as purely of vegetarian origin.

- The Bureau of Indian Standards (BIS) has formulated 'Draft Indian Standards for vegetable capsule shells, cellulose based'. Hydroxypropyl methyl cellulose (HPMC), most commonly known as Hypromellose, is used in the manufacturing of the cellulose-based capsule shell. The draft stated for requirement and test methods of hard vegetable capsule shells for manufacturing.

- Honorable Supreme court of India vide civil appeal no. 5645 of 2003 dated 07/03/2013, the Supreme Court has held that symbols to indicate non-vegetarian or vegetarian ingredients are not required to be printed on the package of a cosmetic or a drug as the latter cannot be treated at par with food articles for labeling purposes.

Regulatory challenges after replacement of gelatin capsules with cellulose capsules:

As gelatin capsules have healthy and approved technology, whereas cellulose capsules developed by new technology with semi synthetic materials. Gelatin is easily digested whereas HPMC is non-digestible.
Cellulosed capsules (HPMC) are mainly used in Nutraceuticals industries and the medicinal formulations, if filled in cellulose capsules will have to be tested for disintegration, dissolution, stability, bioavailability, bioequivalence, compatibility with drugs, machinability etc. Thus, all the modified release dosage form needs to be redesigned in that scenario.
As per Drugs and Cosmetics modified release dosage form would be consider as New drugs or Subsequent new drugs for that every formulation has to get necessary regulatory permission from regulatory authorities. Moreover, any change over from existing Hard Gelatin Capsules to non-gelatin capsules cannot be done arbitrarily and must be supported with 'bridging studies' like compatibility studies, toxicity-bridge and performance-bridge through dissolution/bioavailability/clinical studies.
Also, there are few drugs which belong to Biopharmaceutical Classification system class II and IV having narrow therapeutic & absorption window would require more rigorous bridging studies, to ensure safety and efficacy. These studies would be needed not only in the 'initial' product but also at the end of the

shelf life. Latter would be necessary as polymeric materials like gelatin; HPMC etc. can undergo changes over the shelf life that can affect their performance.

Since, the time taken for the study or tests of bioequivalence of thousands of drugs and combinations and Pharmacokinetics and Pharmacodynamics properties will take several years followed by the long process of regulatory approval from the drug authorities, this could impact all the citizens of this country, as also globally as most countries are dependent on India's generic drugs.

There is a need of complete preparation on below indistinctness prior to consider this move which has multiples of challenges with very minor advantages.

- Do we have the HPMC capsules production capacity to match and then meet the growing demands?
- Do we have any plan to exempt regulatory approval process due to replacement of gelatin capsules with HPMC?
- Do we have any specific guidelines ready with regulatory requirement in terms of safety & efficacy and stability of the modified Dosage form (New Drugs as per D&C Act)?
- Do we have any action plan to minimize the cost of HPMC capsules shell and increase in 'Make in India' production of HPMC capsules?

Hence, request you to kindly considering the complexity and the enormity of the issues involved. As per current scenario, there is no proper beneficial justification to consider the proposal to switch from well tested and proven technology of gelatin based capsules to non-gelatin (HPMC based) capsules. Such a strong move to replace gelatin based capsules with cellulose based capsules may reconsider prior to making it mandatory for entire pharmaceutical industry.

Further, ARAP is looking forward to support your Directorate for further representation of our opinion on the subject matter or any assistance required to make any regulatory policy or guidelines.

Thanking you,

With best regards,

VARUN KUMAR
(Secretary General)

Association of Regulatory Affairs Professionals New Delhi