INTERNATIONAL PHARMACEUTICAL EXCIPIENTS COUNCIL OF INDIA (IPEC INDIA)

Excipient Regulations Perspective & Creation of IPEC India

(Current Regulations & Emerging challenges for excipient regulations in India)

At

ExcipientFest Americas –April 25-27,2016

Monday, 27th April 2016

Renaissance Harborplace Hotel - Baltimore- Maryland USA

By:

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Content of Presentation

CURRENT REGULATIONS

- Agencies, Standards for Drug Regulation in India
- Framework & Responsibilities of the Drug Regulatory Agencies
- Excipient Regulatory and Testing Requirements
- Excipient Information in Drug Approval Applications
- Licensing & Registration of Excipients – Local & Imported
- Regulations for Colorants & Flavors Permissible for use in Drugs in India
- Concerns on Interpretations of Control of Excipients

EMERGING CHALLENGES

- Microbial Limit test for Pharma Raw Materials
- Imported Drug Products compliance to D&C Act & Rules of India
- IP compliance for Imported Excipients
- Nutraceuticals / Dietary-Health supplements Regulatory status

FORMATION OF IPEC INDIA –

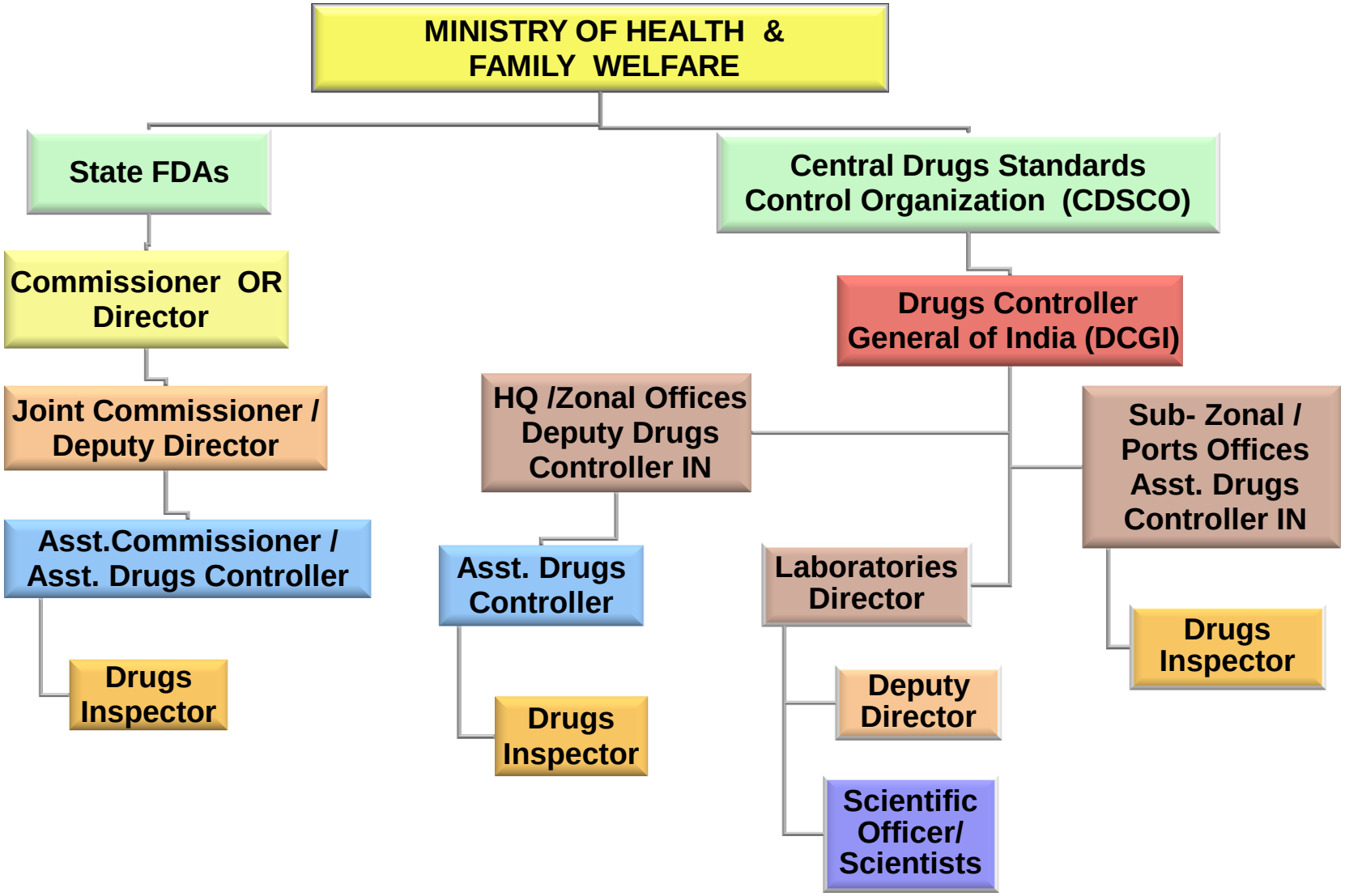
- Vision, Mission, Objectives
- Organization framework & committees
- Educational Initiatives
- Current & long term projects and forthcoming events

Drug Regulatory System - INDIA

- The Indian constitution lists Drugs and Health concurrently as one of its most important segments that is governed by both Centre and State governments under **Drugs and Cosmetics Act 1940 & Rules 1945.**
- Various bodies control Drugs and Health regulations in India :
  - Ministry of Health and Family Welfare (MHFW)
  - Central Drug Standards Control Organization (CDSCO)
  - Drug Technical Advisory Board (DTAB)
  - Indian Council Of Medical Research (ICMR)
  - Indian Pharmacopoeia Commission (IPC)
  - National Pharmaceutical Pricing Authority (NPPA)
  - Central Drug Testing Laboratory (CDTL)
  - Indian Pharmaceutical Association (IPA) *

*** Relates with industry concerns with existing and developing drug regulations**

Regulatory Agency Framework – India



Acts Implemented

- **The Drugs and Cosmetics Act 1940 and Rules 1945 (Applicable to Allopathic/ Ayurvedic & Homeopathic Drugs)**
  - Schedule M – Good Manufacturing Practices
  - Schedule U – Control of Records
  - Schedule L1 – Good Laboratory Practices
- The Drugs and Magic Remedies (Objectionable Advertisements) Act 1954 and Rules 1955
- The Narcotic Drugs and Psychotropic Substances Act, 1985 and Rules1985
- The Poisons Act,1919
- The Drugs Price (Control) Order,1995

Responsibilities – Central and State Authorities

- **CENTRAL DRUGS STANDARD CONTROL ORGANIZATION (CDSCO)**

(a) CENTRAL AUTHORITIES

- **Mainly controls Drugs – Active Pharmaceutical Ingredients and Finished Drug Products. New Drug approvals**
- **Excipients with IP (Indian Pharmacopoeia) claim only are controlled by Regulatory agency.**

- **Central Drugs Standard Control Organization Headquarters** is located at FDA Bhawan, Kotla Road, **New Delhi** 110002 and functions under the Directorate General of Health Services

(b) STATE FOOD AND DRUG ADMINISTRATION

- The regulation, under the Drug and Cosmetics Act, of manufacture, sale and distribution of Drugs is the primary responsibility and it includes granting and renewal of licences of Drug Manufacturing Units
- **Issue various Certificates for Tenders, Exports**
- Many other related functions like Inspection/ audits of drug manufacturing and selling units, control of Narcotic Drug activities, educate consumers on safe use of drugs etc.

Excipients – Regulatory Requirements

- **The Drug Regulatory agencies in India are more focused on Active Drug and its Finished Product - Tablets / Capsules / Syrups / injections etc.**
  - NO specific regulations for Excipients except that they comply to IP or other international compendia. There is a need for further regulation to standardize the approach.
  - No quantity restrictions – no focus on the quantity used if excipient is on any list of acceptable excipients

- **Excipients need to have Precedence of use either in India or any other country. (i.e.; can use U.S. FDA's IID, compendia listings (USP, PhEu, JP, etc..), even FCC to justify acceptability)**
  - References from Martindale or Handbook of Pharmaceutical Excipients also serve as supporting data for approval for intended use of that Excipient.

Excipients – Regulatory Requirements

- **Only those excipients that are claimed or graded as IP (Indian Pharmacopoeia) may be controlled by the FDA.**
  - The manufacturer in that case would need to be registered with FDA and have a Drug manufacturing Licence that is renewable every 5 years subject to inspection by the FDA authorities.

- **There is no mechanism to issue a Manufacturing License to overseas manufacturers of Excipients**
  - Registration of Imported Drugs (includes dual purpose Excipients) – separate regulation (Fee = USD $2500)
  - The manufacturing site and the product would need registration and would involve inspection of the manufacturing facility by the Indian regulators- fees of USD $5000 to be borne by the applicant
  - *No Registration Certificate shall be required under these Rules in respect of an inactive bulk substance to be used for a drug formulation, with or without pharmacopeial conformity.*
  - Can sometimes create customs delays during imports.

Excipients – Testing Requirements

- **Testing of Excipients**
  - **Need to comply with IP if a monograph exists in the compendia.**
    - In case of NO IP claim by manufacturer then it is the User's responsibility to ensure the excipient's compliance to IP monograph & GMP assessment.
  - **In absence of a IP monograph**, compliance to any other International Compendia like USP/ EP/BP/ JP etc.. is acceptable,
  - **For exports** even in-house specifications and validated test methods are acceptable, if the excipient is listed as such with inclusion of the specification & test method, in the drug approval application.

Excipient Information in Drug Approval Applications-1

- **Drug application need to include approximate drug product composition (master formula) including list of excipients used and the Compendial status of each excipient listed.**

- There is no official quantity requirement for excipient used in a drug formulation.

- In case the Drug is manufactured in India for export to countries following WHO regulations/ guidelines then a Certificate of Pharmaceutical Product (COPP) is required from the Local FDA.

- Colorants when used in a Drug formulation the same have to be claimed on the Product label as the common color name as listed under Rule 127 (list of colors permitted for use in drugs) of the Drug & Cosmetic Act & Rules of India.

Excipient Information in Drug Approval Applications- 2

- Excipient manufacturer or country of origin requirements not defined. Specifications define the excipient to be used.
- No notification to local FDA is needed when supplier changes unless the specification is changed.
- Change in excipient or excipient level in a formulation should be notified to FDA with justification for change. (Generally the change should not exceed 10 % of the original approved formulation).
  - The applicant does not have to wait for local FDA approval unless they come back with questions

Licensing & Registration of Excipients – Local & Imported

LOCALLY MANUFACTURED EXCIPIENTS

- **All Locally manufactured Excipients if graded as IP need to be registered with the Local – State FDA in a similar way as a Drug.**
  - This would need approval of the site and the Excipient product with FDA, license to manufacture/ stock and sell or distribute the excipient with a valid Manufacturing License that will be renewable every 5 years subject to FDA inspection.
  - Any Excipient that has a IP monograph and is known to be used for therapeutic purpose but does not have IP claim , need NOT be registered with FDA, however it needs to have a label claim as " NOT FOR MEDICINAL USE" when it is an industrial grade. (i.e.; Glycerin, Castor Oil incidents in the past)

Licensing & Registration of Excipients – Local & Imported

IMPORTED EXCIPIENTS

- **All Imported Excipients for use as an Active Drug need to be registered with the DCGI and also requires an Import License**
  - The product as well as the manufacturing site is to be registered and the registration costs USD $2500 - This is followed by acquiring an Import License.. Both are valid for 3 years
  - This registration & Import license can be obtained by the user or the agent / distributor importing that excipient.
  - Information on Imports (including registration) can be found at links below: http://www.cdsco.nic.in/ AND http://www.cdsco.nic.in/checklist%20import(01.08.2012).pdf

- **The Excipients for Dual purpose – (Active as well as Excipient)** - e.g. Dextrose monohydrate/ Stearic Acid /.Sorbic Acid/ Riboflavin etc., when imported need clearance from DCGI to use as excipient. – **Can be done as one time activity by agents or distributors**

Colorants & Flavors permissible for use in Drugs in India

- **COLORS: Rule 127 of Drug and Cosmetic Act - "List of colors permitted for use in Drugs"**
  - The label on the container of a drug containing a permitted color shall indicate the common name of the color used.
  - Aluminum or Calcium salts (Lakes) of any of the water soluble colors listed under Coal Tar colors are also permitted.
  - Any non permitted or non-listed color for Export use requires drug manufacturer to acquire permission from DCGI for each export batch quantity

- **FLAVORS :**
  - No list of flavors exists as a regulation
  - FEMA GRAS flavors are considered acceptable
  - Testing can be as per that suggested by manufacturer

Colorants/Flavors – Regulations in India

- The Flavors are identified in the drug application but are not required to be mentioned on the drug product Label.
- No test standards are available for analyzing Lake colors & Flavors.
  - List of colors needs to be amended to harmonize with international listings
- Test standards available for dyes - Bureau of Indian Standards (BIS)
- No quantity Restrictions on use of colorants & flavors
- Change in flavor and color is to be notified to FDA – a prior approval is required with amendment to the registered formulation and draft labels if affected.

Concerns – Interpretation of Control of Excipients

- **The Definition of Drug in the Drug & Cosmetic Act includes a statement :** "***All substances intended for use as components of a drug including empty gelatin capsules;"***

- **Lack of specific guidelines or regulations for Excipients to be used in drugs to be marketed in India.**
  - Drug regulation interpreted for Excipients in various ways by users makers and regulators as per their specific requirement & causes conflicts with opinions
  - Lack of clarity over requirement of Drug manufacturing License for Premixed excipient / Atypical actives.
  - Confusion by regulators with testing needs and information on COAs due to comparison with Drugs
    - e.g. Expiry date vs Retest / Re-evaluation date

      Routine vs. periodic testing requirements (even ID tests). No clear guidelines exist.

Concerns – Interpretation of Control of Excipients

- **Lack of specific guidelines or regulations for Excipients to be used in drugs to be marketed in India. (cont.)**
  - Sea and Airport – on many instances, have different opinions on the category under which the Excipient is imported. Left to individual interpretation.
  - Lack of guideline on proper classification of the excipient when both compendial claims for food & drug is available on COA or product labels. This leads conflicts between Custom officials & importer sometimes about higher duty leading to improper classification & duty payment.

EMERGING CHANGES

- Microbial limit test for Pharma raw materials.
- Imported drug products compliance to D&C Act 1940 & Rules 1945 of India.
- IP compliance for imported Excipients – COA to include the same
- Nutraceuticals/ Dietary-Health Supplements (DS-HS) –Regulatory status in India

Microbial limit test for Pharma raw materials

Effective 1st April 2014 the Microbial Limit test is mandatory for all the pharma raw materials as per the India Pharmacopeia 2014.

The Microbial Limit Test Acceptance Criteria for Substances Formulations (Page No: 49 of IP 2014) is given below. These limits are similar to the USP & EP, however the implementation policy of IP is different than that of USP/ EP.

Table 5 – Acceptance criteria for microbiological quality of nonsterile substances for pharmaceutical use

	TAC (CFU per g or per ml)	TFC (CFU per g or per ml)
Substances for pharmaceutical use	10^3	10^2

IP confirmed that these parameters are mandatory and must be reported on the raw material manufacturers' COAs effective 1st April 2014.

Microbial limit test for Pharma raw materials

- **However excipient manufacturers –many of which are not attached to the FDA or IP are not aware of this requirement**.
  - Not all excipients are at risk for micro growth and testing each lot is not practical for those (there aren't enough in-house or external labs that could handle the combined demand). Further, the cost to implement this testing would substantially increase the cost for excipients which would likely be passed on to pharma customers. If incoming raw materials are rejected due to not meeting this requirement, drug production will be impacted.
  - The USP/ PhEur policy in general believes that typically, if you can receive scientifically credible information from your supplier as to why there should not be a microbial concern then routine testing is not required. That is the approach allowed for in the USP and PhEur and is what is typically used to demonstrate compliance along with some type of periodic check that may be in place as a verification.
- Pharma industry interpreting it as per the USP/ PhEur policies currently, however there are some instances when users demand for this compliance going by the regulation.
- IPEC India plans to take this forward along with comments initiated by IPEC Americas & IPEC Federation, USP, a few Pharma related organizations and a couple of excipient manufacturers agreeing to participate in discussions with IP commission.

Imported drug products compliance to D&C Act & Rules of India

- **CDSCO notice of 4 March 2014– for all drugs products imported into India need to comply to the requirements of D&C Act1940/ Rule 1945 – thus enforcing the Expiry date instead of Retest or re-evaluation concept widely used by excipients.**
- It appears that this recent notice could be used to enforce provisions in this to impact excipient and API ingredients since in this Act, any ingredient in a drug is defined as a drug,
  Clarity required if expiry dates are required or whether this may cause varied interpretation by Pharma companies due to lack of clarity in the notice, but in either case, India is changing its ways of enforcements of regulations.
- After some concerns raised by industry with the Customs & Regulatory authorities, for the time being the notice is not being applied to Excipients.
- However a guideline would be preferred from the DCGI on this .

IP Compliance for Imported Excipients

- Growing requirement from Users & Regulators to claim IP compliance for an excipient when an Indian Pharmacopoeia monograph exists for it.
- The interpretation varies between regulators and also between users.
- An overseas manufactured excipient will meet compliance for the country of origin and does not have registration with Indian FDA as no mechanism exists for approving overseas manufacturer.
- Excipient may comply with Testing standards of IP but does not have Indian GMP compliance certification to claim or grade the product as IP.
- Clear guidance is required on this.

Nutraceuticals/ DS-HS – Regulatory status

- **All manufacturers of Dietary or Health Supplements or Nutraceuticals, that were earlier registered under other regulations (Drugs & Cosmetic Act/ Prevention of Food adulteration Act / Ayush/ Bureau of Indian Standards etc) were directed to register under FSSAI.**
  - For their products for which the Food safety had not been evaluated earlier were granted a **No Objection Certificate (NOC) for manufacture & sale for one year only**, within which they had to provide all **data to prove safety and efficacy as food of that product & its individual ingredients**,
  - However this was on case by case basis. A food approval was granted subject to acceptance & approval of the submitted data.

- Although manufacturers provided the required safety data, it was not always possible to complete the review by the regulators in a year due to various reasons. In that case the NOC was extended until the review was completed.
  - In case the safety and efficacy could not match the use as foods, the product approval would not be granted causing a big blow to the already existing business of that product under drug or similar regulation and being marketed successfully.
  - Due to lack of specific guidance on permissibility of ingredients for such category of food there were confusions on the ingredients & their quantities used in the formulations. Codex standards & quantities were referred in that case during reviews.

Nutraceuticals/ DS-HS – Regulatory status

- Thus with focus on Food Safety , the FSSAI rightly initiated & proposed a new regulation for Nutraceuticals, Dietary /Health supplements as they realized that there was need for a specific guidance on this category of food supplements.

- A draft regulation "**Food Safety and Standards (Food or Health Supplements, Nutraceuticals, Foods for Special Dietary Uses, Foods for Special Medical purpose, Functional Foods, and Novel Food) Regulations" was published in early 2015.**
  - Comments were invited from various organizations, regulatory bodies & the industry. The comment period closed in NOV 2015.
  - Council for responsible Nutrition has commented on this draft.
  - An outcome of the comments is awaited.

- *A list of ingredients permitted for use in Foods is published and available on the website of FSSAI :* *http://www.fssai.gov.in/* and it is basically the section 13.6 of CODEX General Standard for Food Additives (CODEX GSFA) list and almost all additives that are permissible globally, are listed there. However the individual food category is to be referred specifically.

***Ingredients complying to International compendia USP/ EP/ JP etc are also permitted for use in this category of foods*.**

FORMATION OF IPEC INDIA

- IPEC INDIA Formation
- IPEC India – Vision / Mission
- Role of IPEC INDIA – Path Forward
- IPEC INDIA Managing Committee & Working Committees
- Matters of attention
- IPEC India & Drug control Authority
- Recent Initiatives of IPEC India & Forthcoming events

IPEC India - Formation

- **IPEC India incorporated in January 2014 as a non-profit organization.**
- **Now a member of IPEC Federation**

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IPEC India - Stakeholders

- Manufacturers
- End Users
- Distributors
- Regulators

IPEC INDIA MEMBERS

AUSTRALIA

USA

IPEC India – Founder Members

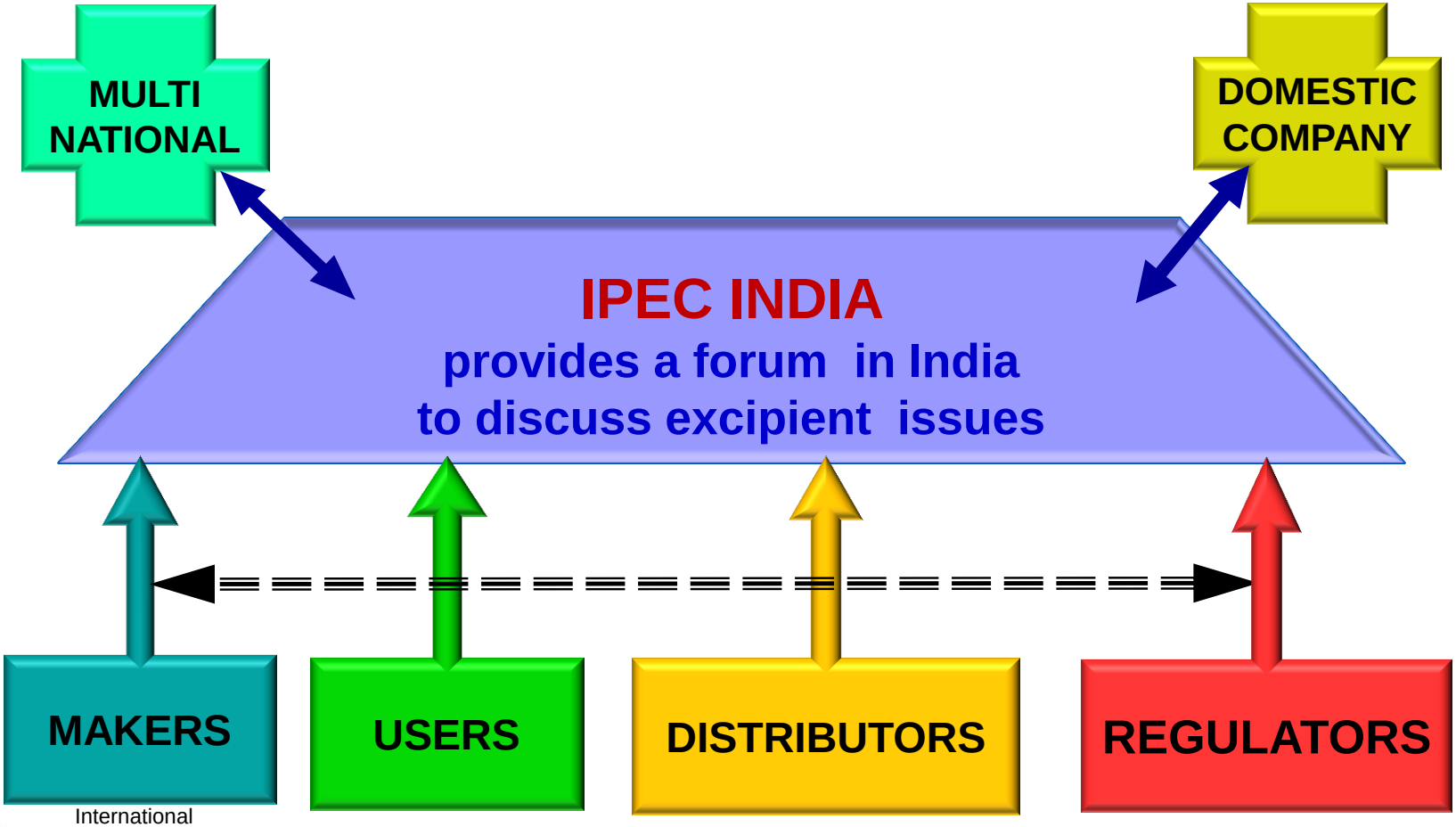
- ACG WORLDWIDE
- BASF INDIA LTD
- COLORCON ASIA PVT LTD.
- DOW CHEMICAL INTERNATIONAL PVT. LTD.
- INDCHEM INTERNATIONAL PVT. LTD.
- LUBRIZOL ADVANCED MATERIALS INDIA PVT. LTD.
- MERCK INDIA LTD.
- MICRO LABS
- SPI PHARMA INC.

OUR MEMBERS @ IPEC INDIA

19 members - excipient manufacturers, distributors & pharmaceutical companies

Formation of IPEC India

IPEC India was formed as a non-profit organization in January 2014



IPEC India Vision

VISION:

To be recognized as the authoritative Indian body for the promotion of quality, functionality and safety of global pharmaceutical excipients.

Developing to be a well –recognized independent association effectively creating awareness in GMP, GLP among excipient users and manufacturers;

Bridging the gaps between government & non- government; existing regulation and the next one to go for improvement, harmonizing the gaps of standards and regulations between local and global.

IPEC India Mission

- **MISSION:**
- **To collaborate with all our stakeholders in order to:**
- **Develop and implement Standards and Regulations that are harmonized with global standards throughout the supply chain.**
- **Create awareness within our stakeholders on current and future Excipients and their related regulations.**

Develop, implement, and promote voluntary guidance and other programs for the world pharmaceutical industry that are designed to ensure continued availability of excipients and related components for finished products that meet the highest appropriate standards for quality, safety and functionality throughout their manufacturing process and supply chain;

Encourage and assist the industry, FDA, the Indian Pharmacopoeia (IP), and other public health and compendial standards for pharmaceutical excipients;

Assist, educate, and cooperate with regulatory authorities, industry organizations and scientific bodies working to advance public health on matters relating to the manufacture, distribution, use, and functionality of excipients.

Objectives of IPEC India

Evaluate existing standards, and develop and proactively promote additional scientifically sound, risk-based standards through internal development and influencing external organizations.

Ensure its continued viability by providing the necessary resources to achieve its objectives.

Maintain and develop external collaborative relationships and establish new ones as appropriate to meet members' objectives.

Implement appropriate regular monitoring of the external factors impacting IPEC and excipients, to inform the membership and other appropriate organizations.

Objectives of IPEC India – contd/…

Develop a promotion and communication program by means of seminars, webinars, workshops, participation in symposiums, exhibitions to inform government, industry, media and the public about excipient issues and our accomplishments.

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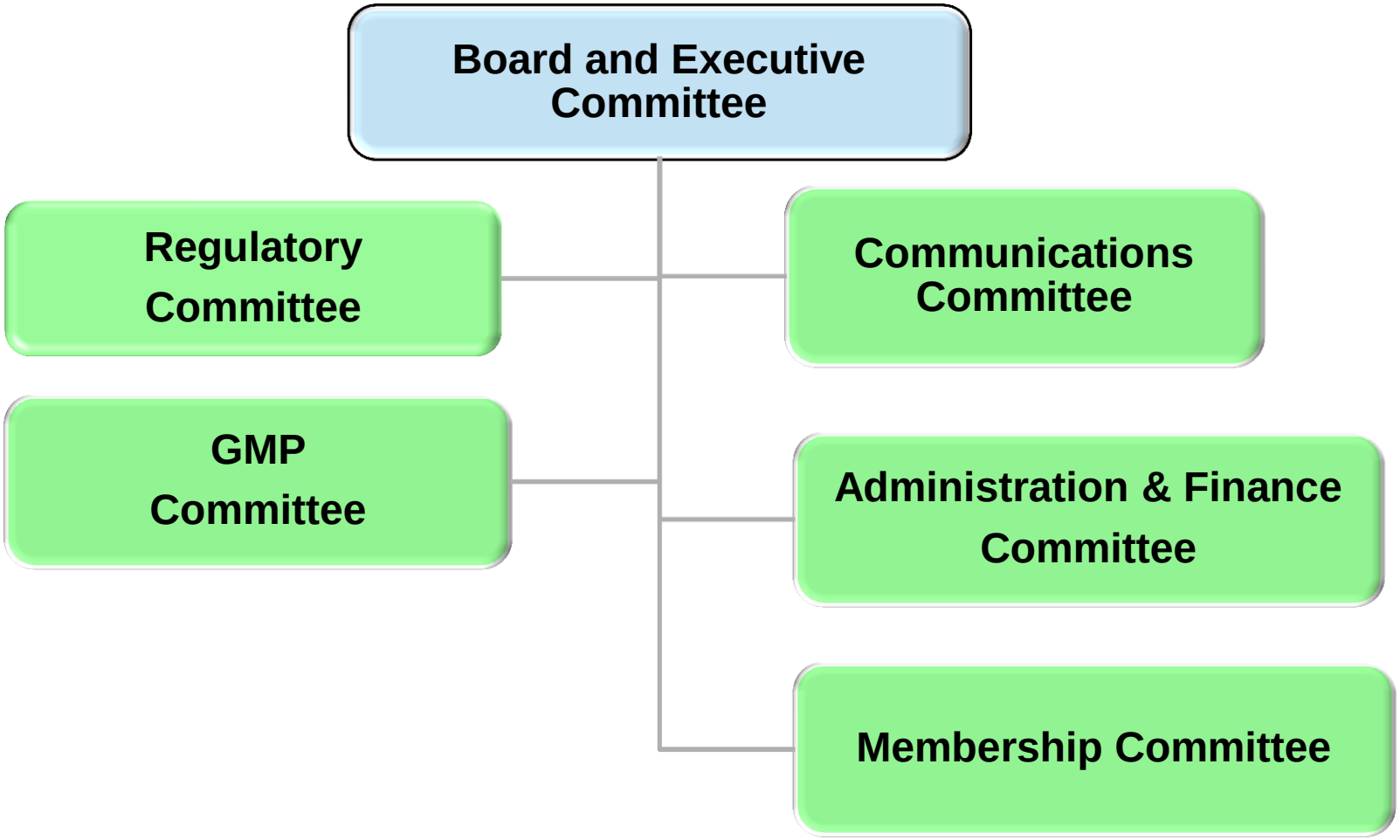
Develop, promote and encourage a science-based risk-management approach to lifecycle management that is appropriate to the maintenance of consumer safety and viable for the supply chain.

Create awareness among excipient manufacturers, distributors and users about the various IPEC Guidelines for the Industry.

IPEC INDIA – Organization Structure



IPEC INDIA – Working committees

COMMUNICATIONS COMMITTEE:

CHAIRMAN

Peter Salazar (MERCK INDIA)

VICE-CHAIRMAN

Vishakha Metkar (COLORCON ASIA PVT. LTD)

MEMBERS:

- Hemant Mhatre (ACG WORLDWIDE)
- Vaishali Tawde (BASF)
- Prashant Chitgopekar (DOW)
- Sudhir Toraskar (EVONIK)
- Narayan Sainathan (INDCHEM)
- Kedar Chikhalikar (LUBRIZOL)
- Seema Kamat (MERCK)

ADMINISTRATION & FINANCE COMMITTEE:

CHAIRMAN:

Ajit Singh (ACG WORLDWIDE)

MEMBERS :

Subodh Priolkar (COLORCON ASIA PVT. LTD)

IPEC INDIA – Working committees

REGULATORY AFFAIRS COMMITTEE:

CHAIRMAN
Vishakha Metkar
(COLORCON ASIA PVT LTD)

VICE-CHAIRMAN
Seema Kamat
(MERCK INDIA LTD)

COMPENDIAL REVIEW SUB-COMMITTEE:

MEMBERS :
- Tejas Gunjikar (DOW)
- Vaibhav Ambudkar (COLORCON)
- Shakila Pai (MICRO LABS)

REGULATORY AFFAIRS SUB-COMMITTEE:

MEMBERS:
- Patricia Shetty (ACG WORLDWIDE)
- Vaishali Tawde (BASF)
- Suneeta Sonawane (BASF)
- Wilbur Vaz (COLORCON)
- Prashant Chitgopekar (DOW)
- Dyaneshwar Jondhale (DOW)
- Nitesh Shah (EVONIK)
- S.M Muddha (MICRO LABS)

IPEC INDIA – Working committees

GMP COMMITTEE:

CHAIRMAN

Kedar Chikhalikar (LUBRIZOL ADVANCED MATERIALS INDIA PVT LTD)

MEMBERS:

- Hemant Mhatre (ACG WORLDWIDE)
- Vilas Kurambhatti (ACG WORLDWIDE)
- Prakash Gadhave (COLORCON IN)
- Mayur Malkan (MERCK INDIA)
- Seema Kamat (MERCK INDIA)

MEMBERSHIP COMMITTEE:

CHAIRMAN:

Narayan Sainathan (INDCHEM INTERNATIONAL PVT LTD)

MEMBERS :

Prashant Chitgopekar (DOW)

Current Priority Projects

New Indian Pharmacopeia requirements

- *Microbial testing for non-sterile / non pharmacopoeial products*

Central Drugs Standard Control Organisation notice:

- *All drugs products imported into India need to comply to the requirements of D&C Act1940/ Rule 1945*

Longer Term Projects

Need for specific guidelines for Several Excipients

Excipient Regulatory & Testing Requirements

Clarity / specific guideline on Excipient Information required in Formulation Approval Applications

Longer Term Projects…. Contd.

Licensing & Registration of Excipients – Local & Imported

Concerns on Interpretations of Control of Excipients

Regulations for Colorants & Flavors permissible for use in Drugs in India

Close Relationship between IPEC India and Drugs Control Authority of India

- **Building a close relationship with the Regulators**.
  - To enhance the manufacturing and quality standards of Excipients in India
  - IPEC India can provide expert knowledge on excipients
  - A direct interaction on excipient issues
  - Create an environment for safe use of quality excipients in drugs.
  - One Honorary Position on the Board for Regulators.

IPEC India – Educational Initiatives

Seminar on
An Introduction to Excipient Regulations In India
Both Generic And Domestic'
Friday,14th November 2014, SciTech Centre, Mumbai

IPEC India – Educational Initiatives

Seminar on
An Introduction to Excipient Regulations In India
Both Generic And Domestic
Friday,14th November 2014, SciTech Centre, Mumbai

IPEC India – Educational Initiatives

"EXCiPACT Awareness Training"
by Allan Whiston, CQP, FCQI, C Eng., MiMechE E,
Member EXCiPACT Board and IPEC Europe GDP Committee
Friday, 13th February 2015, SciTech Centre, Jogeshwari (W), Mumbai.

IPEC India – Educational Initiatives

"EXCiPACT Awareness Training"
by Allan Whiston, CQP, FCQI, C Eng., MiMechE E,
Member EXCiPACT Board and IPEC Europe GDP Committee
Friday, 13th February 2015, SciTech Centre, Jogeshwari (W), Mumbai.

Forthcoming Major events

1ST ANNUAL CONFERENCE
July 2016
(Total Excipient Control)
At
Mumbai

In discussion with the Organizers and Mr Dwight Mutchler.

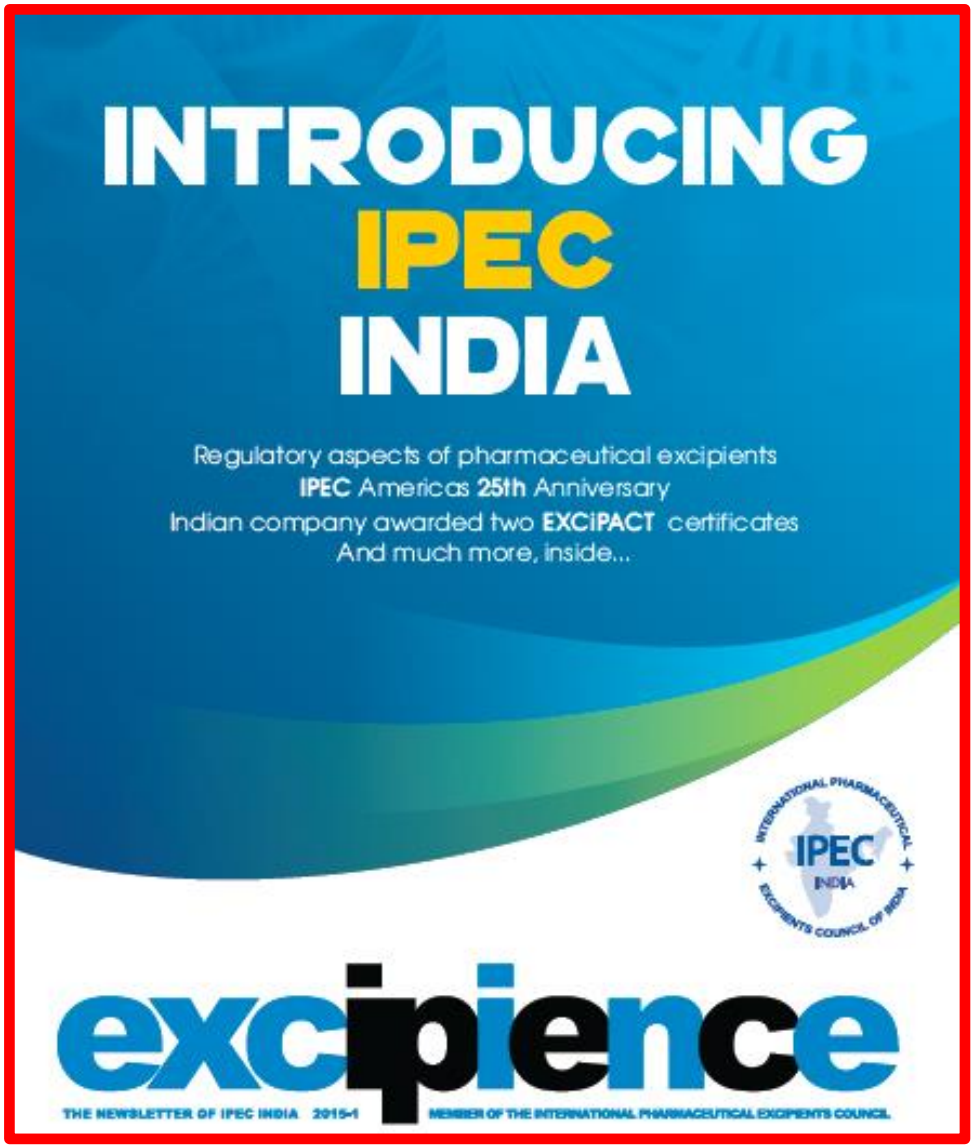
IPEC FEDERATION
EXCIPIENT FEST

Including an EXHIBITION of excipient manufacturers (Indian and Global).

- **Technical Seminars**
- **Students counselling/ consulting to choose appropriate jobs in the industry**

EXCIPIENCE – IPEC INDIA NEWSLETTER

The 1st edition of IPEC India Newsletter "EXCIPIENCE" was published in November 2015



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THANKYou

Your Questions