



Excipient Regulations in India

David R. Schoneker

Director of Global Regulatory Affairs – Colorcon
Vice Chair – Maker and Distributor Relations – IPEC-
Americas

dschoneker@colorcon.com



Outline of Presentation

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



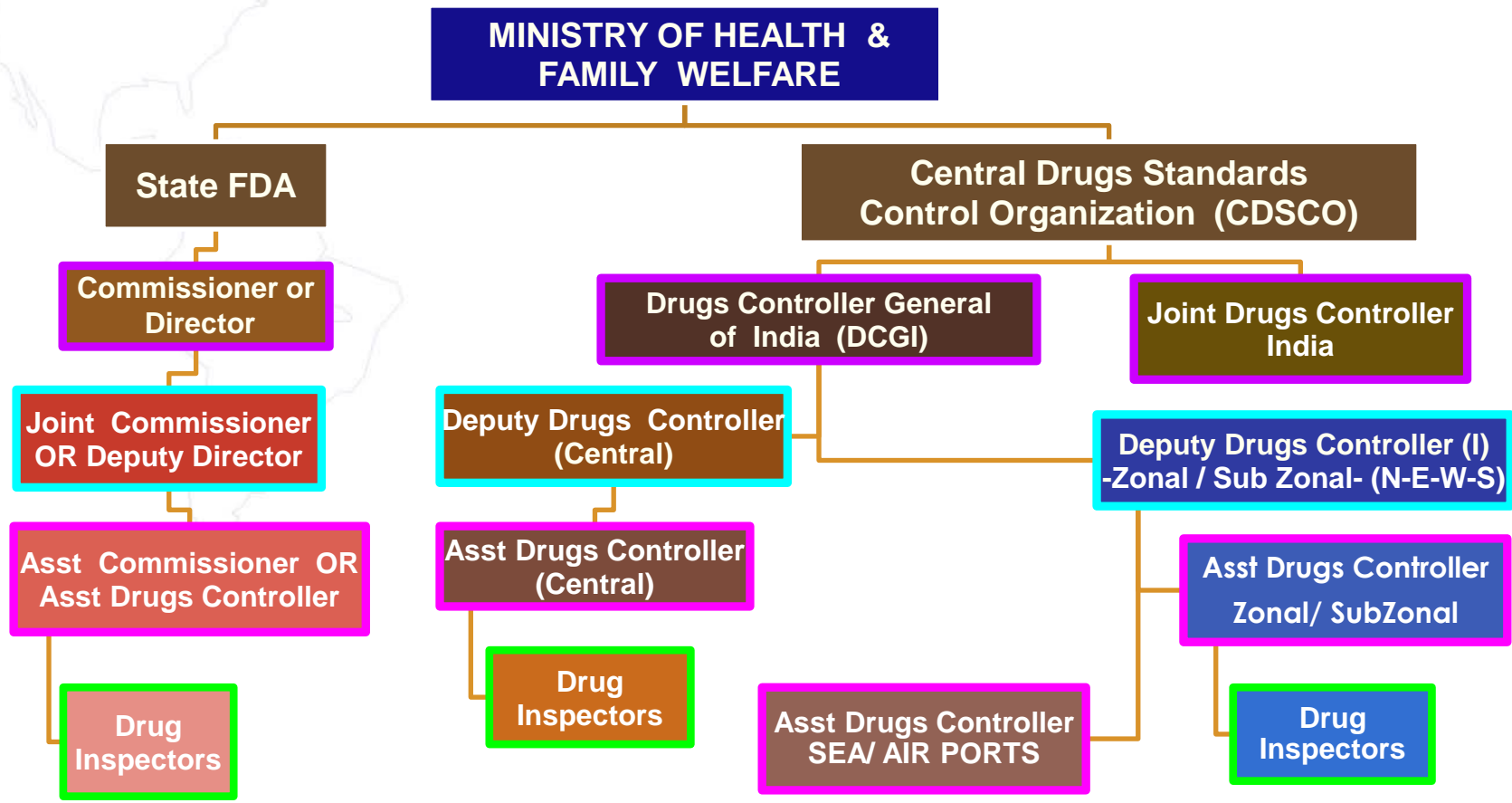
Drug Regulatory System - INDIA

- 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
- The Drugs and Magic Remedies (Objectionable Advertisements) Act 1954 and Rules 1955
- The Narcotic Drugs and Psychotropic Substances Act, 1985 and Rules 1985
- The Poisons Act, 1919
- The Drugs Price (Control) Order, 1995



Responsibilities – Central Authorities

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

- **(a) CENTRAL AUTHORITIES**

- Approval of New Drugs
- Control over the quality of imported Drugs
- Clinical Trials in the country
- Laying down the standards for Drugs
- Drug Controller General of India is responsible for approval of licenses of specified categories of Drugs such as blood and blood products, I. V. Fluids, Vaccine and Sera.
- Coordination of activities for State Drug Control Organisations
- Providing expert advice and uniformity in the enforcement of the Drugs and Cosmetics Act.

Mainly controls Drugs – Active Pharmaceutical Ingredients and Finished Drug Products.

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



Responsibilities – State Authorities

- **STATE FOOD AND DRUG ADMINISTRATION-**
 - Primary responsibility is the regulation, under the **Drug and Cosmetics Act**, of manufacture, sale and distribution of Drugs including granting and renewal of Drug manufacturing unit licences
 - Issue Certificates for Tenders, Exports as listed below:
 - WHO GMP certificate (State FDA issues assurance to WHO GMP)
 - No Conviction Certificate (no criminal/legal issues pending against the firm or employees)
 - Performance Certificate (company risk and performance, GMP problems, etc..)
 - Free Sale Certificate (shows acceptability for use in drugs – similar to U.S. & EU)
 - Schedule M GMP Certificate (follows GMP section of the D&C Act)
 - Many other related functions such as:
 - Inspection/ audits of drug manufacturing and selling units
 - Control of Narcotic Drug activities
 - Education of 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, Ph. Eur., 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 an excipient.



Excipients – Regulatory Requirements

- **Only excipients that are claimed or graded as IP (Indian Pharmacopoeia) may be controlled by the FDA.**
 - Manufacturer is required to be registered with the FDA and have a Drug manufacturing licence which, subject to FDA inspection, is renewable every 5 years.
- **No mechanism exists to issue a Manufacturing License to overseas excipient manufacturers**
 - Registration of Imported Drugs (including dual purpose excipients) – separate regulation (Fee = USD \$2500)
 - The manufacturing site and the product must be registered and inspected of by the Indian regulators - fees of USD \$5000 to be borne by the applicant
 - *No Registration Certificate required under these Rules in respect of an inactive bulk substance for use in a drug formulation, with or without pharmacopoeial conformity.*
 - Can sometimes create customs delays during imports.



Excipients – Testing Requirements

- **Testing of Excipients**
 - **Need to comply with IP if a compendia monograph exists.**
 - In case of NO IP claim by manufacturer then it is the User's responsibility to ensure the excipient's compliance to IP monograph.
 - Only relevant for testing requirement, does not include GMP assessment
 - **In absence of an IP monograph**, compliance to another International Compendia such as USP/ EP/BP/JP etc.. is acceptable, if the excipient is listed as such in the drug approval application.
 - **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
 - For excipient monographs desired by the manufacturer or required by regulators to be included in IP, the IP Commission reviews the testing details, validation, etc.. Testing is performed in an IP laboratory to verify tests.



Excipient Information in Drug Approval Applications

- The applications for drug approval need to list the excipients used in the drug preparation.
- The drug approval application is required to include the approximate composition of the drug product (master formula) including the quantity and the Compendial status of each excipient used.
 - No clear guidance exists regarding how to handle pre-mixed excipients at this time.
- For exports it is possible to list excipient in- house / compliance specifications (e.g. a mix of certain USP/ EP/ IP test parameters)
 - these have to be submitted to the FDA along with the application for drug approval.



Excipient Information in Drug Approval Applications

- No mention of excipient manufacturer or country of origin is required. Specifications define the excipient to be used. No notification to FDA is needed when supplier changes unless the specification is changed.
- Change in any excipient or level of an excipient in a formulation may simply be notified to FDA with the justification for the change. The applicant does not have to wait for FDA approval unless they come back with questions



Licensing & Registration of Excipients – Local & Imported

- **All Locally manufactured excipients graded as IP need to be registered with the Local – State FDA in a similar way as a Drug.**
 - The excipient manufacturing site and the product require approval by the FDA. A license is required to manufacture/ stock and sell or distribute the excipient. The manufacturing license is 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

- **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.cdsc.gov.in/> AND [http://www.cdsc.gov.in/checklist%20import\(01.08.2012\).pdf](http://www.cdsc.gov.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**



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.*
 - *This generally creates conflicts between users- makers- regulators*
 - *Lack of clarity over requirement of drug manufacturing License for premixed excipient (possible area for IPEC India involvement to clarify)*
 - *Information on COAs generally a confusion for Regulators as it is compared to that for drugs. Confusion over 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 - always have different opinions on the category under which the Excipient is imported. Left to individual interpretation. (possible area for IPEC India involvement to clarify requirements)*
 - *Deliberate attempts to reclassify the excipient under a food category that allows them to extract extra duty by illogical interpretation of claims of both Food and Drug compendias (USP vs. FCC) from COA*



Colorants & Flavors permissible for use in Drugs in India – 1

Rule 127 of Drug and Cosmetic Act - "List of colors permitted for use in Drugs "

COMMON NAME OF COLOUR	Colour Index Number	CHEMICAL NAME
GREEN		
Quinazarine Green S.S.	61565	1, 4-bis (p-Toluino) anthra-quinone
Alizarin Cyanine Green F	61570	Disodium salt of 1, 4-bis (O-sulfo-p-Toluino) anthra-quinone
Fast Green F.C.F.	42053	Disodium salt of 4-[[4-(N-ethylpsulfobenzylamino)-phenyl]- (4-hydroxy-2-sulfonium phenyl)- methylene] [1-(N-ethyl-N-p-sulfobenzyl] 2, 5-cyclohexadienimine]-
[* * * Green S- Omitted by G.O.I. Notification No.GSR 753(E) dt 4.11.1999.]		
YELLOW		
Tartrazine	19140	Trisodium salt of 3-carboxy-5-Hydroxyl-1-p-sulfophenyl-4-p-Sulfophenylazopyrazole
Sunset Yellow FCF	15985	Disodium salt of 1-p-sulfophenyl Azo- 2-naphthol-6-sulfonic acid
Quinoline Yellow WS	47005	Disodium salt of Disulfonic acid of 12-(2-quinolyl)-1, 3-indandione
RED		
[* * * 'Amaranth' -Omitted by G.O.I. Notification No.GSR 753(E) dt 4.11.1999.]		
Erythrosine	45430	Disodium salt of 9-O-carboxypheny l6-hydroxy 2,4-5,7-tetriodo-3-isoxanthone
Eosin YS or Eosine G	45380	Disodium of salt of 2,4,5, 7-Tetrabromo 9-p-carboxyphenyl-6-hydroxy 3-isoxanthone.
Toney Red or Sudan III	26100	1-p-phenylazophenylazo-2-naphthol.
Ponceau 4 R	16255	Trisodium salt of 1-(4-sulpho-1-1-Naphthylazo)-2 naphthol-6 : 8-disulphonic acid.
Carmoisine	14720	Disodium salt of 2-(4-sulpho-1-nap-Thylazo)-1 naphthol-4 sulphonic acid
* * 'Fast Red'- Omitted by G.O.I. Notification No.GSR 753(E) dt 4.11.1999.]		



Colorants & flavors permissible for use in Drugs in India – 1

COMMON NAME OF COLOUR	Colour Index Number	CHEMICAL NAME
BLUE		
Indigo Carmine	73015	Disodium salt of indigotin-5 : -5 Disulphonic Acid
Brilliant Blue FCF	42090	Disodium salt of 4-[{4-(N-ethyl-psulfobenzylamino)- phenyl }-(2-sulfonium phenyl)-methylene)-1-(N- ethyl- N-psulfobenyl)/_¥2, 5-cyclohexadienimine
ORANGE		
Orange G	16230	Disodium salt of 1-phenylaze-2- naphthol-6,8-disulfonic acid.
BROWN		
Resorcin Brown	20170	Monosodium salt of 4-p- sulfophenylazo-2-(2, 4xylylazo)-1, 3 resorcinol.
BLACK		
Naphthol Blue Black	20470	Disodium salt of 8-amino-7-p-nitrophenylazo-2- phenylazo-1-naphthol-3, 6-disulfonic acid.

Those highlighted in pink do not have any E- number so not permissible in EU.

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 label on the container of a drug containing a permitted color shall indicate the common name of the color as well as the API used.
- Aluminum or calcium salts (Lakes) of any of the water soluble colors listed under coal tar colors are also permitted.
- Only Rule 127 listed colors permitted for use in drugs intended for marketing in India .
 - Any non permitted or non-listed color for export use requires drug manufacturer to acquire permission from DCGI for each export batch quantity. Every batch using the non permitted colorant needs DCGI clearance based on the permission by the Health authorities of the country of export. A procedure for this clearance can be obtained from the DCGI.
- Quinoline yellow which is listed is not the same as D&C Yellow #10. Rule 127 specifically mentions it to be the disulfonated derivative version which matches the E104 standard (suitable for EU also).
- Amaranth, Green S and Fast Red E are banned for use in drugs.



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.
- 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 – for colorant a prior approval is required



IPEC Offers Excipient Stakeholders a Regional Voice with Global Influence



IPEC Federation

- Established in 2009,
- based in Belgium / made up of regional IPECS



IPEC-Americas

- North, South and Middle Americas
- Partnership with Sindusfarma (Brazil) and SaFybi (Argentina)



IPEC-Europe

- Europe, North Africa, Middle East



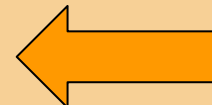
IPEC Japan



IPEC China



IPEC India (being formed)





Formation of IPEC India

- IPEC India is currently being formed to provide a forum in India for both multi-national and domestic companies to discuss excipient issues between makers, users and distributors as well as regulators
- After significant investigation into the legal structures necessary to form an appropriate trade association, the registration documents have been filed and currently awaiting final confirmation of registration
- IPEC India is expected to be formed as an official trade association by the end of 2013
- Once formed, additional member companies will be able to join the association
- The first activity that IPEC India will organize will be an Excipient Control Conference in mid-2014



IPEC – India Vision Statement

- To be the recognized credible and dependable Non-profit organization on representing pharmaceutical excipients manufacturers, users distributors to address industry issues.
- To be recognized by the industry, regulatory authorities, compendia, standard setting bodies and academia as a leading Non-profit organization that develops and recommends appropriate voluntary manufacturing and safety standards for excipient manufacturers, distributors and users of excipients.



IPEC – India Mission Statement

- To collaborate with our partner regional IPEC groups to:
 - 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.



IPEC – India will:

- 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.
- Implement appropriate regular monitoring of the external factors impacting IPEC and excipients, to inform the membership and other appropriate organizations.
- Maintain and develop external collaborative relationships and establish new ones as appropriate to meet members' objectives.



IPEC – India will:

- 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.
- 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.



LIST OF INITIAL MEMBERS OF THE IPEC INDIA COMMITTEE

Sr. No.	Name	Company Name	Designation
1.	Mr. Ajit Singh	ACG Worldwide	Chairman
2.	Mr. Subodh Priolkar	Colorcon Asia Pvt Ltd	Regional Managing Director – South Asia
3.	Mr. Narayan Sainathan	Indchem International	Director
4.	Mr. Peter Salazar	Merck India Pvt. Ltd.	General Manager – Pharm-Chem Solutions
5.	Ms. Veena Singh	DOW Wolf Cellulosics India	Regional Commercial Manager
6.	Mr. S. M Mudda	Micro Labs	Executive Director- Technical & Operations



Companies planning to join IPEC India

1	Abbott Laboratories	12	ICN Pharmaceuticals
2	ACG Worldwide	13	Indchem International
3	Ashland	14	Johnson & Johnson
4	BASF India	15	Merck India Ltd
5	BSI Group	16	Micrto Labs
6	Cipla Ltd	17	Noveon
7	Colorcon	18	Pfizer
8	DFE Pharma	19	Ranbaxy Laboratories
9	Dow Wolff Cellulosics	20	Sanofi aventis
10	Evonik (Degussa)	21	Schimadzu
11	GSK Pharmaceuticals	22	USV Ltd



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Your Questions

