Role of Excipients in Pharmaceutical Formulations

By

Dr.A.Ramkishan

Deputy Drugs Controller (India)

CDSCO Zonal Office, Hyderabad

Outline

- Evolution of Indian drug legislation
- Functions of CDSCO and SLAs
- Preamble of drugs and cosmetics ACT 1940
- What are Nitrosamines ?
- Background information on excipients
- Definition of Excipients and its classification of excipients
- Importance of product development
- Nitrosamines in excipients & Drug products
- Indian Pharmacopoeia 2022 General Chapter 5.11- Nitrosamine impurities
- Risk based inspections
- Routine GMP violations during Risk based Inspections (RBI)
- Conclusions

Evolution of Indian Drug Legislation

Preamble

To **regulate** manufacture, sale, distribution and import of drugs, cosmetics, Biologicals, medical devices and other products.

Objective

The Objective of Drugs & Cosmetics Act is to **ensure** that public are supplied with safety, efficacy and quality of drugs (Sec. 3b).

Basic Philosophy

The basic philosophy of Drugs & Cosmetics Act is that the **manufacturer is responsible for the quality** of drugs manufactured by them and the **Government/Regulatory Agencies will monitor** the quality of drugs by periodic inspections of the manufacturing and sales premises for confirmation to the provisions of Drugs & Cosmetics Act and monitoring the quality of drugs moving in the market by carrying out post market surveillance.

Principle

The principle on which the Drugs & Cosmetics Act function is by a system of licensing under which all the activities involved in manufacture, sale and distribution of Drugs & Cosmetics are **controlled**.

Drug Regulatory System in India

Drug is in concurrent list of Indian Constitution. It is governed by both Centre and State Governments under the Drugs & Cosmetics Act, 1940 and Rules 1945 thereunder.

Functions of CDSCO

- Approval of new drugs and clinical trials
- Import Registration and Licensing
- License approving of Blood Centres, LVPs, Vaccines, r-DNA Products, Medical Devices & IVD's (CLAA Scheme)
- Amendment to D &C Act and Rules
- Banning of drugs and cosmetics
- Grant of Test License
- Testing of New Drugs

Functions of State Licensing Authorities

- Licensing of Manufacturing Site for Drugs including API and Finished Formulation
- Licensing of Establishment for sale or distribution of Drugs
- Approval of Drug Testing Laboratories
- Monitoring of Quality of Drugs and Cosmetics marketed in the country
- Investigation and prosecution in respect of contravention of legal provision
- Recall of sub-standard drugs

Drugs and Cosmetics Act and Rules

Objective:

To ensure safety, efficacy and quality of

Drugs

Biologics

Medical Devices

Cosmetics

Veterinary Drugs.

Drugs and Cosmetics Act

Principle:

"Through system of licensing"

Basic Philosophy:

- **Manufacturers are responsible for quality of drugs manufactured by them**
- **Government Regulatory Agencies will monitor the quality of drugs by**
  - periodic inspections of the manufacturing and sales premises for confirmation to the provisions of Drugs & Cosmetics Act
  - monitoring the quality of drugs moving in the market by carrying out post market surveillance.

Chapters of D&C Act:

Title	Contents
Chapter -1	Definitions
Chapter -2	Statutory committee's (DTAB, DCC) and laboratories
Chapter -3	Import of drugs and cosmetics
Chapter -4	Manufacture, sale and distribution of drugs and cosmetics
Chapter -4A	Ayurveda, Homeopathy, Siddha and Unani drugs
Chapter- 5	Miscellaneous eg. Powers to give directions, Special Courts, offences by Govt. Departments etc.

Importance of Excipients & Its formulations

- Specialty excipients are used to produce dosage forms that can reduce the number of doses by modifying the rate of drug release or improve drug delivery by targeting drug release in a specific region in the gastrointestinal tract where drug absorption is the highest.
- These excipients play an important role in converting a pharmacologically active compound to an elegant pharmaceutical product with enhanced provision for therapeutic use. It is generally assumed that excipients are pharmacologically inactive and are deemed safe in patients.
- The functional roles of pharmaceutical excipients include modulating bioavailability and solubility of APIs, increasing the stability of APIs in the dosage form, maintaining the osmolarity and/or pH of the liquid formulations, preventing dissociation and aggregation, etc.
- The main classes of excipients are the antioxidants, coating materials, emulgents, taste- and smell-improvers, ointment bases, conserving agents, consistency-improvers and disintegrating materials.

How do you choose excipients for formulation?

How to select the right excipient ?

- Dose.
- Particle Size.
- Flow Properties.
- Bulk Density.
- Moisture Content.
- Hygroscopic.
- Excipient Compatibility.
- Compatibility

Advantages of Natural excipients & its Bio-availability

- Nature and composed of repeating monosaccharide units, hence they are non-toxic & Economic.
- They are affordable, and their production cost is less than synthetic material.
- Excipients are generally pharmacologically inert, but can interact with drugs in the dosage form and the physiological factors at the site of absorption to affect the bioavailability of a drug product. A general mechanistic understanding of the basis of these interactions is essential to design robust drug products.

Quality of Excipients

- Excipient quality is, therefore, best expressed as conformance to GMPs as well as to compendia or a specification and consistent composition, lot to lot. Consistent composition within each lot is also an expression of excipient quality, but oftentimes such consistency is difficult to achieve without a blending step.
- Ideally, an excipient is pharmacologically inactive, non-toxic, and does not interact with the active ingredients or other excipients. However, in practice few excipients meet these criteria.
- Examples include gelatin, cellulose, cellulose derivatives, polyvinylpyrrolidone, starch, sucrose, glycerine, sorbitol solution and polyethylene glycol. Dry binders are added to the powder blend, either after a wet granulation step, or as part of a direct powder compression (DC) formula.
- In the case of liquid oral dosage forms, the choice of excipient rests on factors such as chemical and physical compatibility and stability of the product along with ensuring acceptable organoleptic product properties (i.e., taste, color, consistency, etc.

Excipients in Pharmaceutical Formulations

- An excipient is a pharmacologically inactive substance formulated alongside the active pharmaceutical ingredient of a medication. Purposes served by excipients: • Provide bulk to the formulation. Facilitate drug absorption or solubility and other pharmacokinetic considerations.
- Glidants - Fumed silica, Talc, Magnesium carbonate
- Lubricants - PEG, Magnesium Stearate, Stearic acids and its derivatives
- Sweeteners - Sucrose, saccharine, Aspartame, Sorbitol
- Binders - Gelatin, Cellulose, Polyvinylpyrrolidone, Starch, Sucrose, PEG, Cellulose and its derivatives

Differences Between Raw materials & Excipients

- Raw materials are input substances used in both chemical synthesis and processing and include buffers, cleaning agents, common solvents and commonly used synthetic starting materials such as amino acids. Excipients are substances which are used as ingredients in pharmaceutical formulations such as tablets and capsules.
- Raw materials like glycerine for manufacturing of liquid oral preparations such as, Cough, Allergy, Analgesic and Anti emetic drug products is very important for identity testing as per USP-NF monograph includes testing of di-ethylene glycol & ethylene glycol in either the propylene glycol and di-ethylene glycol stearates.
- In the pharmaceutical industry, raw materials are generally categorized, into three major types: Raw Materials of Excipients, Raw Materials of API, and Raw Materials of Packaging. Excipients, also called drug carriers, are the carrier material in any drug.
- FDA guidance for industry issued in May 2023 for the production of effective and safe liquid dosage forms.

Importance of Glycerine

- Glycerol is popular as an excipient in cough medicines because it serves multiple functions; acting as a sweetening agent (0.6 times the sweetness of sucrose), a solvent, lubricant, antimicrobial, humectant, and preservative.
- In the pharmaceutical industry, it's widely used as a lubricant and humectant and as an essential ingredient in many cough syrups, ointments, expectorants, anesthetics, and lozenges. Manufacturers also use glycerin to make drug capsules.
- Glycerol is a component of most cough syrups, and although it is often thought of only as a solvent or thickening agent in cough syrups, it may be a major component for the efficacy of cough syrups due to its special properties of lubrication, demulcency, sweetness, and acting as a humectant.

PEG & DEG

- Pharmaceutical-grade PEG is used as an excipient in many pharmaceutical products, in oral, topical, and parenteral dosage forms.
- physical properties of diethylene glycol make it an excellent counterfeit for pharmaceutical-grade glycerine (also called glycerol) or propylene glycol, and has caused many deaths in different countries.
- For Example : In 1937, a Tennessee drug company manufactured sulfanilamide dissolved with diethylene glycol, to create a liquid alternative of this drug. The company tested the new product, Elixir sulfanilamide, for viscosity, appearance and fragrance. At the time, the food and drug laws did not require toxicological analysis before releasing for sale. When 105 people died in 15 states during the months of September and October, the trail led back to the elixir, and the toxic potential of this chemical was revealed

Incidents with DEG

- 1969 – South Africa – 7 Children died due to Un acceptable level of DEG
- 1985 – Spain – 5 Patients died due to anuric kidney failure.
- 1986 – India – Bombay Hospital, 21 patients died and the discovery of glycerin contaminated with 18.5% v/v of DEG.
- 1990 – Nigeria – 47 Children died due to Kidney failure - Assumed that DEG was used as a substitute of propylene glycol.
- 1992 – Bangladesh – 337 Children died – Paracetamol syrup contaminated with diethylene glycol.
- 2020 - India- Ramnagar – J&K – 17 children died due to Cough syrup contained 34.97% of diethylene glycol, which resulted in poisoning and subsequent renal failures.
- 2022 – Gambia - Maiden Pharmaceuticals Limited, Sonepat in India – 99 children died.

Background on DEG cases

The above cases reveal the following similarities

1. Manufacturers of the liquid drug products that contained contaminated glycerine did not perform full identity test on raw material including tests to quantify the amount of DEG presence and to verify the purity of glycerine received.
2. Manufacturers relied on certificate of analysis (COA) provided by supplier of glycerine.
3. Copy of COA on the letter heads of distributer not by the original manufacturer of the glycerine.
4. So regulators need to focus on thorough vendor audits, vendor qualification and vendor selection with respect to meeting GMP of excipients to ensure compatible liquid formulations.

Regulatory requirements

USP provides 3 parts identity test for Glycerine

1. Infrared Absorption spectroscopy
2. Gas chromatography to quantify limit of DEG & EG even though glycerin identify by IR Spectra which is not suitable for detection of quantification of DEG & EG (Limit is NMT 0.10 %).
3. So, representative samples of each shipment of each LOT of glycerin intended to be used as a component in the drug product manufacturing must be tested and found to meet the DEG & EG limits included in the identity test in the USP glycerine monograph before used in drug product manufacturing.
4. Raw materials should comply CGMP defined by section 501(a)(2)(B) of the FD&C Act.

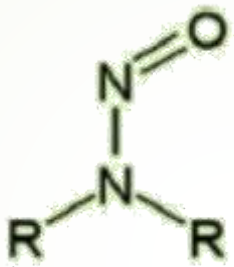
Recommendation to safeguard the quality and safety of medicines from DEG/EG contamination

FDA recommends the following:

1. Ensure the specific identity analysis for each LOT which includes limit test for DEG/EG incorporates testing of samples from al containers of all LOT's of a high-risk drug component before the high-risk drug component is used in the manufacture of drug products.
2. For high-risk drug components where the DEG/EG tests are not included in the identification tests of the USP monograph for the components, The manufacturer used suitable equivalent procedure for quantify DEG/EG use as safety limit of NMT 0.101 %.
3. Drug manufacturer's maintain the current knowledge of their supply chain for high-risk drug components.
4. All personal in manufacturing facilities should aware of proper DEG/EG contamination testing and potential hazards is this testing is not done.
5. Accurate COA from original manufacturer should be ensured for each component of LOT shipment and also testing is done by a reliable supplier.

What are Nitrosamines ?

- N-nitrosamines are a class of organic compounds that are associated with a potential for a significant carcinogenic risk



- Nitrosamines are present in various foods, beverages, as well as water; however, their presence in medicines is unacceptable
- The presence of N-nitrosamines in final drug products has become a global issue

Medicinal products recalled due to nitrosamine issues

- Ranitidine
- Nizatidine
- Metformin
- Valsartan
- Candesartan cilexetil
- Irbesartan
- Olmesartan medoxomil
- Losartan potassium
- Varenicline

Source of Nitrosamines in medicinal products

- The formation of N-nitrosamines (NDMA) in medicinal products is influenced by three factors:
  - Nitrosating agent: Regents, solvents, starting material
  - Secondary or tertiary amine: API
  - Appropriate conditions (for example elevated temperatures, acidic conditions, liquid phase) for the aforementioned to react.

- Presence of NDMA in sartans has been associated with the use of N,N-dimethylformamide as a solvent and sodium nitrite as a reagent during synthesis
- NDMA was formed in metformin tablets due to the use of dimethylamine (DMA) in the drug substance synthesis and the concomitant presence of nitrite in excipients.
- N-nitroso-varenicline in varenicline tablets was formed by the reaction of the amine functionality of the drug with a nitrosating agent, which is probably nitrite present as an impurity in excipients

Nitrosamines in Excipients

- The risk of the presence of nitrosamine compounds within excipients itself is very low
  - Amine containing excipients such as triethanolamine.
  - Amino Acid Excipients such as L-Histidine, L-Proline, L-Arginine
- Many excipients contain traces of nitrites that can result in formation of nitrosamines under specific conditions within the drug product.
- Low impurity levels in excipients become utmost importance to mitigate nitrosamine issues in medicinal products

Nitrosamine Impurities in Drug Products From Sources Other Than API Contamination:

excipients at ppm levels:

- Corn starch
- Cross carmellose sodium
- Cross povidone
- Hypromellose
- Lactose monohydrate
- Magnesium stearate
- Microcrystalline cellulose
- Povidone
- Sodium starch glycolate,
- pre-gelatinised starch,
- potable water(0.2ppm).

- Potential reactions within the formulation matrix during stability/shelf life (e.g., presence or generation of acidic conditions, moisture, and heat)

N-nitrosamine impurities issues throughout the world

Date	Action in and around country
6 June 2018	**Zhejiang Huahai informed by potential customer of impurity in its valsartan API**
20 June 2018	Zhejiang Huahai tells customers to put use of its valsartan API on hold after preliminary investigation
25 June 2018	Zhejiang Huahai tells customers of presence of NDMA in its valsartan API
26 June 2018	Information related to the presence of NDMA in valsartan from Zhejiang Huahai is disseminated within the Rapid Alert Network
28 June 2018	EU network holds the first Incident Review Network (IRN) and the first Rapid Alert Network (RAN) teleconferences
5 July 2018	EC triggers Article 31 review of valsartan medicines; EMA announces start of review and recalls on its website
9 July 2018	**EDQM suspends Zhejiang Huahai's valsartan CEP (CEP 2010-072)**
2 August 2018	EMA publishes preliminary risk assessment for NDMA in medicines containing Zhejiang Huahai's valsartan API
3 August 2018	**Taiwan Food and Drug Administration alerts regulators of valsartan API from Zhejiang Tianyu and Zhuhai Rundu Pharma**
9 August 2018	**US Food and Drug Administration (FDA) announces the detection of NDMA in valsartan API from Hetero Labs**

- USFDA August 2023 document issued for intake limits for Nitrosamine Drug Substances Related Impurities (NDSRI's).
- NDSRI's can potentially form in API's when nitrosating agents are present in the API manufacturing process or when API's undergo processing steps that can potentially induce their formation such as fluid bed drying at an elevated temperature & jet milling because these can create favourable conditions in which nitrogen oxides can react with at risk API's.
- Because the presence of NDSRI is predominantly associated with drug products rather than API's.
- ICH M7 (R2) is recommend the use of structure activity relationship of nitroso compounds and also concepts to assess and classify mutagenic and carcinogenic impurities.

CDSCO ACTIONS

19.07.2018 Issued a office order by DCGI vide F.No IMP/MISC/82/2018-DC to all port office for sampling of all consignments importing from ZH

- Show cause issued to RC holder & all importer (around 12 members) M/S Etha chem, MH
- Feb.2019 cancelled Zhejiang Huahai, Zhejiang Tianyu and Zhuhai Rundu
- 04.10.2020 Issued a office order by DCGI vide F.No IMP/MISC/82/2018-DC to conduct a investigation to all Zones
- Samples drawn sent to IPC
- API distributed etc.

भारतीय भेषज संहिता आयोग
स्वास्थ्य एवं परिवार कल्याण मंत्रालय, भारत सरकार
सैक्टर २३, राज नगर
गाजियाबाद २०१००२ (उ. प्र.), भारत

INDIAN PHARMACOPOEIA COMMISSION
Ministry of Health & Family Welfare, Government of India
Sector 23, Raj Nagar
Ghaziabad 201002 (U.P.), INDIA

डा. राजीव सिंह रघुवंशी
सचिव-सह-वैज्ञानिक निदेशक

Dr. Rajeev Singh Raghuvanshi
Secretary-cum-Scientific Director

F.No. T.11015/01/2020-AR&D

Date: October 27, 2022

NOTICE

Subject: Clarification on General Chapters of the Indian Pharmacopoeia (IP) 2022-regarding.

Indian Pharmacopoeia Commission (IPC) has published the Indian Pharmacopoeia (IP) 2022 and Hon'ble Union Health Minister released the 9th edition of IP 2022 on 1st July, 2022 in Vigyan Bhawan, New Delhi. In IP 2022, several new monographs and general chapters have been introduced while several others are revised to meet the current analytical and regulatory requirements.

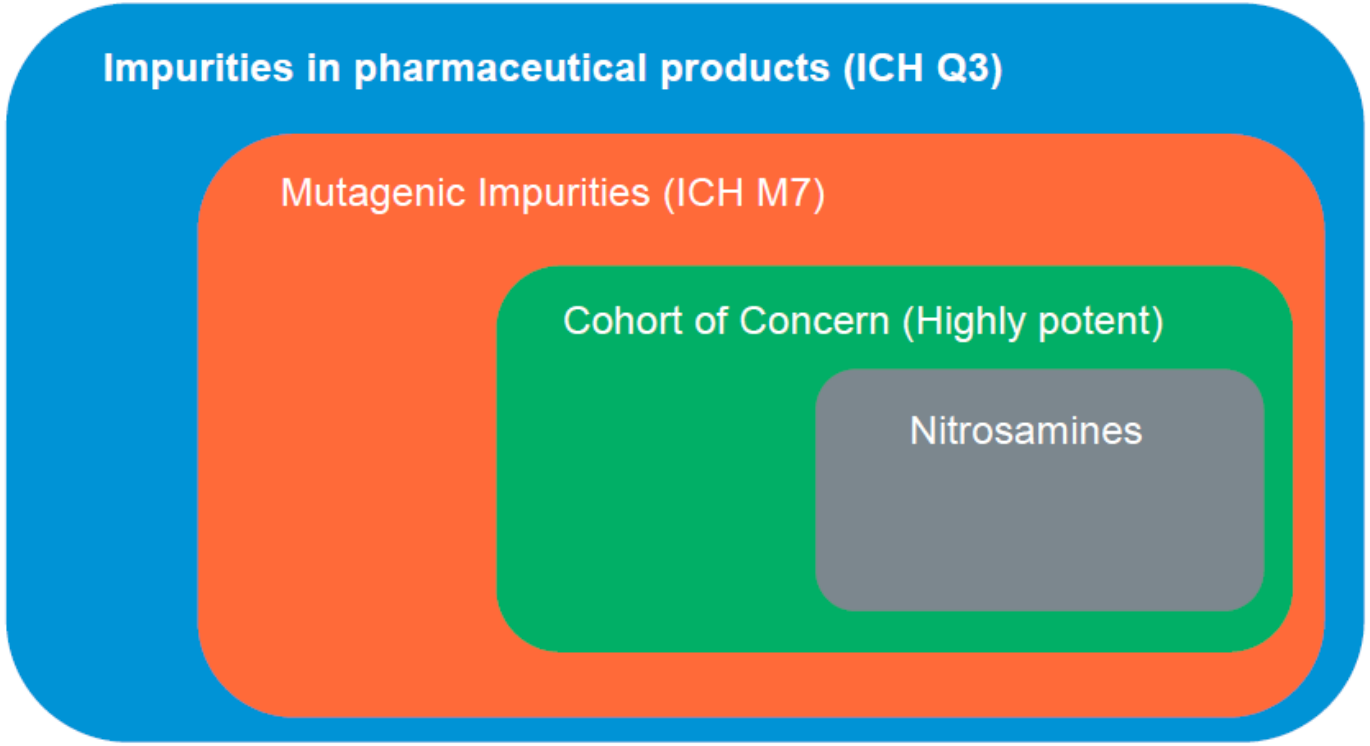
After the release of IP 2022, IPC has received several enquiries from the stakeholders on implementation and compliance of new and/or revised pharmacopoeial text. In order to address the enquiries of the stakeholders, clarification on following general chapters of the IP 2022 is compiled and issued:

S. No.	General Chapter in IP 2022	IPC's Clarification
1.	General Chapter 2.5.4 (i) Uniformity of Dosage Units	IPC has introduced a general chapter on 'Uniformity of Dosage Units' in harmonization with other pharmacopoeias under section 2.5.4 (i) on page 361, Volume I of IP 2022. This chapter is presently introduced in IP 2022 for information and awareness of the stakeholders and is not referred in the individual monographs and, therefore, remains non-mandatory requirement. However, stakeholders may adopt this chater before its implementation is made mandatory by IPC.
2.	General Chapter 5.10 Elemental Impurities	IPC has introduced new general chapter on 'Elemental Impurities' on page 1204, Volume I of IP 2022 for information and awareness of the stakeholders and is not referred in the individual monographs. Therefore, it remains non-mandatory requirement. However, stakeholders may adopt and implement this general chapter as an alternative to test on heavy metals as per the provisions of the IP General Notices. IPC will gradually replace test on heavy metals in the individual monographs to make elemental impurities mandatory from the next edition of IP (i.e. IP 2026).
3.	General Chapter 5.11 Nitrosamine Impurities	IPC has introduced new general chapter on 'Nitrosamine Impurities' on page 1210, Volume I of IP 2022 for guidance of the stakeholders which is also referred in sartan API monographs of the IP. However, it is expected that stakeholders adopt this general chapter for determining the nitrosamine impurities in other drugs as well, wherever deemed appropriate and necessary.

Yours sincerely,

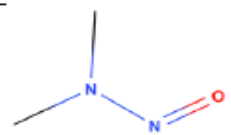
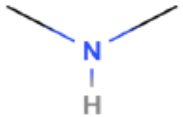
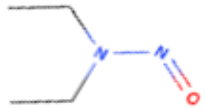
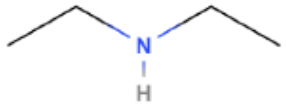
(Dr. Rajeev Singh Raghuvanshi)

Impurities in Pharmaceutical Products



Primary Packaging Materials:

- condensation. *N-nitrosamines was caused by reaction of* **nitrocellulose** in the **lidding foil** with amine constituents of **printing ink.** These impurities were, in some cases, transferred to the drug product during **the heat-sealing blistering process** via vaporization and condensation.
- Novartis recalled
- **Avoidable** by eliminating **nitrocellulos**e as the responsible nitrosating agent in the lidding.

N-Nitrosamine	NOx source	Amine source	Amine nitrosated by NOx	Critical compound combination
 NDMA	Nitrocellulose lidding foil	Printing ink	 DMA	Lidding foil/printing ink
 NDEA	Nitrocellulose lidding foil	Printing ink	 DEA	Lidding foil/printing ink

Information on Nitrosamine Guideline

- As per the recent guideline NDSRI's i.e Nitrosamine Drug substance related impurities these are unique to each API's and Each Excipients and the recent guideline provides the Recommended Acceptable Intake limits for NDSRI's.
- These impurities generally from in the product through Nitrosation of API's which are having the Secondary and Tertiary amines when exposed to residual nitrites present in the Excipients which are used in the formulation.
- The major reasons for the generation of Nitrosamines are introduction of Nitrous acid, Nitrites and Amines during the synthesis of API or Excipients.
- These nitrosamines are classified into 5 Potency Categories for NDSRI's based on the Average Intake.

Information on Nitrosamine Guideline

Potency Cateogory	Recommended Average Intake (AI) ng/day	Remarks
1	26.5	This limit is for most potent highly carcinogenic impurity i.e N-nitroso diethylamine (NDEA) and it should be consumed less than the 26.5 ng/day, previously it was 18 ng/day.
2	100	Here 2 Impurities are most potent and carcinogenic i.e N-nitroso dimethyl amine (NDMA) should be consumed 96ng/day and NNK (4-methylnitrosamino)-1-(3-Pyridyl)-(1-butanone)
3	400	Remaining all Nitrosamine should be with in this limits.
4	1500	
5	1500	

Compiled Data of RBI as on 28.08.2023

sr no		No. of Firms / Labs Inspected	SCN	SPO	Cancellation of Product/ category permission (firm wise)	Suspension of Product/ Category Permission (firm wise)	WL	WIP (firms in which final action is awaited after SCN)
1	Total (Phase-1)	78	68	11	22	17	20	10
2	Total (Phase-2)	47	40	18	10	11	1	16
3	Total (Phase-3)	40	14	6	1	0	0	7
4	Total (International complaints)	14	13	7	3	03	0	4
	Total	179	135	42	36	31	21	37
Note: PTL inspected -28								
SCN – SHOW CAUSE NOTICE, SPO – STOP PRODUCTION ORDER, WL-WARNING LETTER, WIP – WORK IN PROGRESS; PTL-Public Testing Laboratory								

Non-compliances - from Manufacturing Firms:

- Infrastructure deficiency to prevent cross contamination
- Faulty design of manufacturing and testing areas
- AHUs were not installed
- Missing qualified Technical personnel & noticed with ineffective training.
- Manufacturing and Testing activity was not documented adequately.
- No water system for liquid oral dosage form mfg plants.
- No validated procedures for manufacturing & testing.
- Raw material vendors are not approved and frequently changed.
- Raw material/ excipients were not tested – poor vendor qualification
- Non performance of Microbial testing for OSD.
- No Stability chambers/ stability testing.
- Pharma product quality review not conducted.
- Lack of QRM implementation for risk mitigation.
- Lack of self-inspection system and internal quality audit system
- Poor documentation and data integrity issues.

Non-compliances - From Public Testing Laboratory (PTL)

- Data integrity (Results manipulated with sample weight, extra integration of sample peak, less integration of impurity peak and manually deletion of unknown peak etc.)
- Technical personnel were not trained.
- Issuance of test report without testing of samples.
- No raw data, chromatograms, audit trail, retention samples.
- Non availability of reference standards and working standards.
- Working standards received from manufacturer without COA & official source.
- No regular Calibration/qualification of equipment.
- Lack of track and trace system for documents
- Lack of track and trace system for samples
- Poor QRM for risk mitigation
- Lack of GLP manual as per Schedule L1
- Poor documentation practices

Excipient:

Excipients are the Inactive ingredients used as a carriers for the Active ingredients in various Pharmaceutical dosage forms.

The resultant Biological, Chemical, Physical or Pharmacological properties of the drug products are directly affected by the excipients chosen and their concentration in drug product and their interactions with API.

Ideal Properties of Excipients

- No interaction with the Drug
- Cost effective
- Pharmacologically Inert
- Stable for Handling
- Feasible

Classification of Excipients

Based on the nature and the mode of application Excipients are classified as

- Fillers and Diluents
- Disintegrants
- Binders
- Glidants
- Lubricants
- Coating agents
- Colouring agents
- Solubility and Bioavailability Enhancers
- Controlled release Polymers
- Preservatives
- Sweeteners etc..,

Pharmaceutical Product development

As per the ICH guideline Q8 (R2) the pharmaceutical product development includes the following factors to establish a robust formula.

1. Defining the Quality Target Product Profile (QTPP)
2. Identifying the Potential Critical Quality Attributes (CQA's)
3. Identifying the proper Risk Assessment
4. Establishing the Design Space
5. Designing the Control strategy
6. Product life cycle management and continual improvement

Pharmaceutical Product development

From the above six parameters the important factor which correlates to Pharmaceutical excipients is Critical Quality attributes (CQA's):

Critical quality attribute (CQA):

CQA is a Physical, Chemical, Biological or Microbiological property or a characteristic that should be within an appropriate range to ensure the desired product quality.

- CQA's are the combination of Critical Process Parameters (CPP's) and Critical material attributed (CMA's). Here the CMA's are associated with the Drug substance, Excipients, Intermediates (In-Process materials).
- In CMA's we have to consider the

1.Drug-Excipient compatibility – The excipient using in the formulation should not make the Active ingredient degradation under set of temperature and Humidity conditions.

Pharmaceutical Product development

- The concentration of Excipient using in the formulation is one of the most important factor because the excipient concentrations makes the Pharmaceutical systems under stable conditions by not generating any unknown impurities, maintaining the purity of the drug substance 100% complaining to the Quality, Safety and Efficacy of the Pharmaceutical system.
- So many guidelines has been given by the regulatory agencies across the globe with respect to pharmaceutical excipients usage in the finished pharmaceutical product to maintain the Quality, Safety, efficacy of the product to have a heathy nations in the world.

The following are the few examples of Guidelines given to the Pharmaceutical Industry.

1. Safety pharmacological studies for Human Pharmaceuticals
2. Guideline for the assessment of systemic exposure in Toxicity studies and Pharmacokinetics.
3. Guideline for testing the Genotoxicity of Pharmaceuticals.
4. The guideline for the changes to be done with respect to Excipients concentrations after product approval i.e SUPAC (Scale up and Post approval changes).
5. The recent burning topic in the Pharmaceutical industry is presence of Nitrosamine Impurities in the Pharmaceutical products includes both in API's and Excipients.

Conclusions

- Indian legislation is in- line of International guidelines
- Promoting ease of doing business under make in India initiative
- Proactive regulators for promoting industrialization
- Being a hub of Biotech industries, API's, High number of Written Confirmation certificates and 262 WHO-GMP certified units under CDSCO, Hyderabad Zone
- Carrying out all RBI's under crash programme as per the directions of DCG(I) and JS(R) to focus on quality for achieving patient centric effects in clinical practice.
- Implementation of upgraded Schedule M 2018 guidelines in alignment of WHO-TRS Guidelines going to be effectively implemented as per the directions of MoH&FW, India.
- Implementation for submission of BA-BE data in respect of BCS Class II & IV products before product endorsement by Licensing Authorities.
- Excipients are not regulated in India however effective QA/QC vendor selection is important while selecting excipients in Drug formulations to avoid Drug Drug interactions and also to have more compatibility with respect to excipients used in the formulations for achieving patient safety and product stability is very important.

Hon'ble DCGI Dr. Rajeev Singh Raghuvanshi

The fruit of SILENCE is Prayer
The fruit of PRAYER is Faith
The fruit of FAITH is Love
The fruit of LOVE is Service
The fruit of SERVICE is Peace
Enjoy peaceful life

"Value has a value only if its value is valued"


Thank you