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Applying of the Manufacture, Storage and Import of Hazardous Chemicals Rules for the pharmaceutical industry in India with reference to the US-FDA and other regulations – A review

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Abstract
In the globalized world, innovation of the new drugs has resulted in the increase in the operational facility of the pharmaceutical industry, further the existing and new industries, which are expected to reach $130 billion by 2030, as India is eyeing to become third largest economy in the world under the present leadership of Mr. Narendar Modi, prime minister of India. India produces 60 % of generic drugs, which is the highest in the world. India follows strict guidelines for complying with the legal requirement for manufacturing, storage and importing of the chemicals, which are required for the manufacturing of the consented drugs. In this regard on 27th November 1989 the ministry of environment and forest has enacted the manufacturing, storage, import of hazardous chemicals (MSIHC) rules 1989, which was amended in the year of 2020. Initially there were sixteen rules and eight schedules but due to its amendment it has become to 20 rules and 12 schedules. All these rules and the schedules are applied to the pharmaceutical industry in India. These rules, which covers the procedure for getting the approval of the site, getting the authorization for the operational facility of the pharmaceutical industry, various hazards identification and its mitigation, submission of the safety reports to the concerned authority, various was of reporting the major accidents, handling of the onsite and off-site emergency in the pharmaceutical industry. An overview of the schedules, which are applied to the various MSIHC rules, has been covered in this review. The application of the MSIHC rules were correlated with the US-FDA current good manufacturing practices (CGMP) and its importance has been stressed. Further we have also correlated with the other regulations such as the toxic substances control act (TSCA) 1976 for the importing of hazardous chemicals into the USA. All these acts, rules, and regulations, which are having stringent standards for controlling the activities of the drug manufacturing facility to achieve highest quality and safe handling of chemicals during the manufacturing of the consented drugs.

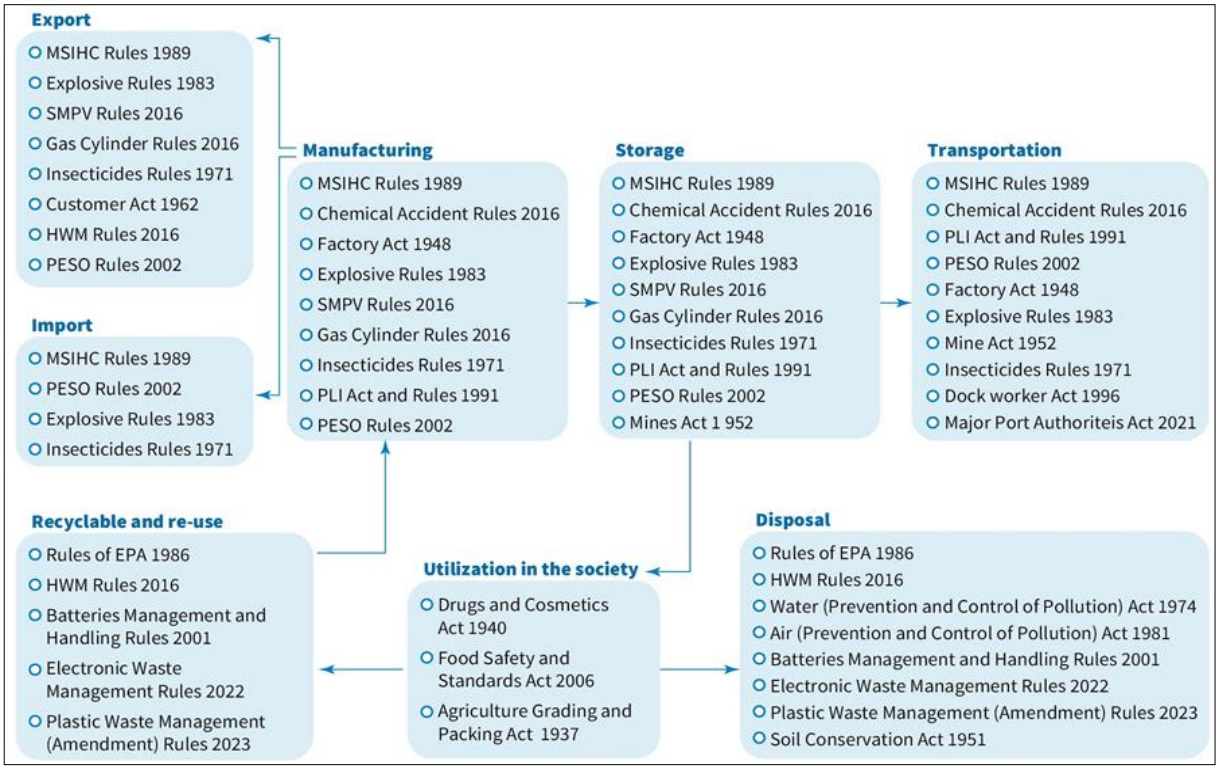
Keywords: MSIHC rules, US-FDA, CGMP, TSCA, quality and safety

Introduction

Pharmaceutical industries are leading contributors to the growth of the national. Further India has involved in supplying the drugs across the globe, which has resulted in saving the life of the millions of people. Globally India supplies about 50 % of vaccines (Excler *et al*., 2021) [14], 40 % generic medicines to the United States of American (USA) (Kaygisiz *et al*., 2019) [20] and 25 % of all different kinds of medicines to the United Kingdom. Further 80 % of antiretroviral drugs are manufactured in India, which has resulted in combating deadly human immune deficiency virus, which is known as acquired immune deficiency syndrome (AIDS). In the recent global pandemic COVID - 19, which has shaken the world by killing more than 3 million people according to world health organization (WHO), Indian scientist has developed vaccine for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which are known as Covaxin and Covishield, which has been major break brough for the scientific community in restricting the spread of the virus across India and globe, which has been reported by Chavda *et al*., 2022 [8], further he has also informed that 60 % of the vaccines used for fighting against the deadly SARS virus has been manufactured in the India, so India has greatest respect in the global community. The government of India has sent free consignments of Covaxin and Covishield to African and other underdeveloped countries free of cost as a good will gesture (Sharma, 2022) [36]. Keeping all the above points India is known as the "Pharmacy of the world", which produces medicines and injections in low cost and high quality to the global community. Many of the Indian Pharmaceutical companies has been approved by international drug authorisation agencies such as united states federal drug authority (US-FDA), European union good manufacturing practices (EU-GMP) and Pharmaceutical medical drug agency (PMDA) (Kumar *et al*., 2023) [24]. India pharmaceutical industries, which follow strict guidelines for handling and storage of the chemicals, which are used for manufacturing the lifesaving drugs. There are different government bodies in India, which govern the manufacturing, storage, export, import, transportation, use, recycling and disposal rules are enacted by various Acts and rules (Fig. 1). The Manufacturing, Storage, and Import of the Hazardous Chemicals rules (MSIHC) 1989 has to be followed during the manufacturing, Importing, exporting, storage and transportation (Fig. 1). The handling of the hazardous chemical and solvents used for the manufacturing of the drugs in the Indian pharmaceutical industry follows the guidelines, which are laid by the MSIHC rules 1989, which was enacted on 27th November 1989 by the ministry of environment and forest (MOEF) and its powers were conferred under the section 6, 8 and 25 of Environment protection act (EPA) 1986 (No. 29 of 1986).

The MSIHC Rules 1989, which consist of sixteen rules and eight schedules, which was amended in the year 2000, which has been increased to 20 rules and 12 schedules, which can be applied for getting the approval of the site,

import and storage of the chemical, which are used for the manufacturing of the drug, finally these manufactured drug is supplied after getting approval from the central drugs standard control organization (CDSCO), which is regulatory body in India (Yadev *et al*., 2021), which comes under the directorate general of health services, Ministry of health and family welfare having its headquarters in new Delhi. There are nine, seven, eighteen. Seventeen and six offices of Zonal, sub-zonal, port offices, central laboratories and mini labs, which are spread across the various parts of the country, which are controlled by CDSCO, which follows the drugs and cosmetics act and rules of 1940, which is amended on 31st December 2016. CDSCO is the body which conducts the clinical trials for their quality of the domestic and imported drug, which is supplied into the country. CDSCO will coordinate with various regional offices, which are there in each state to bring uniformity in enforcing the drug and cosmetics act and its regulation. Similarly, the federal government has passed the controlled substance act (CSA), which has come in to active from the year of 1971, which has resulted in the increase of the manufacturing, import, export, distribution and dispensing of the controlled substances in America (Gabay, 2013) [15], in order to achieve these goals of the



Note: MSIHC – Manufacturing, storage import of hazardous chemicals, SMV – Static and mobile pressure vessels, HWM – Hazardous waste management, PESO – Petroleum explosive safety organisation, PLI – Public liability and insurance and EPA – Environmental protection act.

Fig 1: Application of rules and regulation for manufacturing, storage, transportation, export, import, utilization in society, disposal, recyclable waste in India

manufacturing, import export, distribution and dispensing of the controlled substances must be registered with the federal drug authority (FDA) in America. The FDA has come into existence for the process validation of the drugs, which are manufactured in the United States of America (USA) (Almeter *et al*., 2022) [2], which follows attributable, legible, contemporaneous, original and accurate (ALCA). There are principal guidelines for maintaining the data integrity for the drugs, which are manufactured in the pharmaceutical industry, USA (Khin *et al*., 2020; Rattan, 2018) [33]. The CSA, which has three titles, Title I, which deals in providing the rehabilitation programs for the drug abusers, Title II deals with the registration and distribution of the controlled substances and Title III deals with the import and export of the controlled substances. MSIHC rules 1989, which cover Title II and III of the CSA of the federal government. The FDA, which ensures the quality of the drugs, which are manufactured inside the country and the drugs, which are imported should follow the guidelines of the current good manufacturing practices (CGMP), which are stated in the codes of federal regulation (CFR). The 21 CFR part 210 and 211, which deals with the manufacturing, safety, strength of purity with respect to its quality and packing of the drugs, which are done through the reverse laminar air flow (RLF) technique to avoid cross contamination of the final product. The five main components of the CGMP are five p, which consist of people, procedures, process, product and premises. The long term unresolved CGMP violations by the US manufacturing drug companies is known as "16 black holes" (Almeter *et al*., 2022) [2]. From the beginning of the year of 1980, the USFDA has involved in the approving of the innovation of the generic equivalent drugs, which are in the form of an online resource is known as orange book (US-FDA Orange book, 2022) [42]. In order to meet the demand pressure requirement for the manufacturing of drugs in the US, which has resulted in cutting the cost of manufacturing and shifting the 80 % of its drug manufacturing units to the Asia-Pacific region (Almeter *et al*., 2022) [2]. The US-FDA will be giving three months' time for the inspection of the manufacturing facility, in many of

the cases, the translators will assist them during the inspection (Almeter *et al*., 2022) [2]. The drug inspection by US-FDA is carried out based on the reviewing of the batch manufacturing records (BMR), sampling procedures and testing of the quality of the drugs (Kumar & Kamaraj, 2024; Patil *et al*., 2023; Sharma et. al., 2023) [24, 25, 32, 37]. Although in the year of 2021 the US-FDA announced that the agency is planning to conduct unannounced inspection for the US-FDA drug manufacturing facilities in China and India. The government accountability office (GAO) has announced that it has published 67 pages books for conducting the foreign inspection for the various drug manufacturing facilities around the globe, in this regard the US-FDA has informed that it will resume the inspections from February 2022 (Mukherjee, 2023) [28], they are also using artificial intelligence algorithms for the clinical validation (Khunte *et al*., 2023) [22]. Other regulatory bodies around the world are Medicines and Health care products regulatory Agency (MHRA) of United Kingdom, European Directorate for Quality of Medicines (EDQM) of Europe, Therapeutic Goods Administration (TGA) of Australia, Japanese Ministry of health, Labour and Welfare (MHLW) of Japan, Health Canada (HC) of Canda, Agency National degradation Vigilance Sanitaria (ANVISA) of Brazil and Medicines Control Council (MCC) of South Africa.

Methodology

The MSIHC rules 1989, which includes the amendment for the year of 2000 has been applied for following the rules in getting the approval for the drug manufacturing site, various threshold limits of chemicals, which are to bs stored in manufacturing facility, safety reports submission to the authority by the occupier, its approval from the concern authority and obtaining permission for the operational activity to run the manufacturing facility for the consented drug of the pharmaceutical industry in India has been presented according to laid rules of MSIHC 1989, which includes the on-site and off-site emergency planning to tackle the emergency situation in the hazardous industry. The rules of MSIHC 1989 with reference to the US-FDA and other regulations has been applied in this review article. It deals with the in-depth aspects with respect to the rules and regulation, which are applied for the drug manufacturing facility in India. The outline view of the twelve schedules with respect to the MSIHC 1989 has been included and its importance has been stressed.

Results and Discussion

The list of twenty rules as per the MSIHC rules 1989 along with its amendment made in year of 2000, which are as follows

Rule One is short title and commencement called as Manufacturer, storage and import of hazardous chemicals rules 1989, date of publication by official gazette was 27th November 1989 and it has been amended in the year of 2000 by increasing the rules and their schedules. Syeda (2020) [39] reported that rules, regulations, and acts will help us improve the sustainability of the business and it will have sound framework in handling of the hazardous chemicals. These rules in India will cover all the chemicals, pharmaceuticals, polymer, cosmetics and other industries in different sectors, which are involved in the manufacturing, importing, storing and handling of hazardous chemicals. US-FDA 21 CFR section 21.1, which defines the scope of the regulation of the CGMP for the finished goods. The US-FDA 21 CFR part 5 deals with organizational address contacts, which includes address of the headquarters, chief counsel of food and drug administration office and FDA public administration were provided in part 5 (1100), 5 (1105) and 5 (1110). Such a type of information, which will have open access and make it easy for the occupier for the startups to contact the officer for the various queries which they may have. It would have been better if the contact address information details of the authorities of the various states had been provided in these MSIHC rules in schedule 5. The US-FDA has specific website and its online, as it is open to the public with the new updates whereas the MSIHC rules 1989 are domain specific and online information with updates are recommended in the futuristic point of view as India is eyeing to become the third largest economy in the world.

Rule Two, it deals with various definitions, which are used in the various sections are a. “ACT” - The Manufacturer, Storage and Import of Hazardous Chemicals Rules 1989 has been evolved from the EPA 1986 (29 of 1986). b. “Authority” is given in column 2 of schedule 5, c. Export – Pharmaceutical manufactured drugs, which are taken out of India d. Exporter – The manufacturer of the drugs of the pharmaceutical company have been taken outside India under approval of various legal authorities, e. Hazardous chemicals are i. The chemicals, which are listed in part I of schedule 1, which are listed in column 2 or part II of schedule 1, ii. Chemicals, which are listed in column 2 of schedule 2 and iii. Chemicals, which are listed in column 2 of schedule 3, f. Import – Bringing chemicals into India from outside world, g. Importer – The occupier brings the chemicals from outside India for manufacturing the licensed drugs of the pharmaceutical industry, h. Industrial activity – Consented drugs are manufactured, h (i). The activity in the pharmaceutical industry, which has been carried out by using various equipment’s such as reactors, centrifuges, dryers, agitated nutsche filter, multi milling, Jet milling and shifter. Various chemicals, which are used in the manufacturing of the active pharmaceutical ingredients (API), the active ingredients, which are mixed in the formulation to form a consented drug. Which are resulted due to the organic or inorganic reaction synthesis, which are listed in schedule 4, h (ii). Isolated storage – which refers to the chemical storage of the day storage tanks, which are known as tank farm area. The various hazardous storage of the chemicals, which include Toluene, Isopropyl Alcohol, Methanol, Ethyl Acetate, Acetone, Ethanol, Cyclohexanone, Aniline, Mono Chloro benzene, 2-Methyl tetrahydrofuran, hydrogen and chlorine, h (iii). Pipeline – The pipeline is not explained in the MSIHC rules, we have followed Indian standard IS 2379 (1990) colour coding for the various pipelines, which are used in the Intermediate block (IM block), outside IM block, finished goods block (FG block), Research & Development block (R&D block), stores block, pilot plant block and adjacent to the Effluent treatment plant (ETP), i. Isolated storage - The chemicals, which are stored in the tank farm area with their threshold limits, which are specified in the schedule 2, j. Major accident – It is an accidents, which happens in the occupational environment,

which leads with the loss of life or the injuries caused inside the process equipment's or outside the process equipment's, further the incidents / accidents caused due to the explosion of process equipment's, exposure to the toxic emissions from the process, fugitive emissions leading to the dangerous environment, which results in an on-site or an off-site emergency situation leading to the stoppage of the operations of the production activities, j (a). Major accident hazard (MAH) installations – The chemicals and the solvents, which are stored in the day tanks, equipment's or in the pipeline are within the stipulated threshold limit quantities, which are specified in the column 3 of schedule 2 and 3. k. Pipeline – The equipment and the pipe line are used for transferring the hazardous chemicals, which does not include flammable gases as per column 2 of part II of schedule 3, l. Schedule – It is appended to the rules and regulations, m. Site – It is an occupational environment, where the hazardous chemicals, solvents, operational equipment and various process utilities such as chilled brine, colling tower water, hot water and stream, which are given to the jacket of the process equipment as per the instructions, which are given in batch management record (BMR). n. Threshold quantity – i. Hazardous chemicals, which are specified in column 2 of schedule 2, for which the quantities are specified in the corresponding entry of column 3 and 4, ii. The various hazardous chemicals, which are specified in column 2 of part I of schedule 3 with their threshold quantity specified in column 3 and 4, iii. In the case of the substances of a class specified in column 2 of part II of schedule 3, the quantity of all the substance is specified In column 3 and 4. Similarly in the recent draft of the Chemical (management and safety) rules 2020 of India, which states that chapter 1 of section 2 has more than fifty definitions (CMSR, 2020), although some of the definitions, which were similar to the MSIHC rules are schedule, Import, Importer, Industrial activity, isolated storage, major chemical accident, pipe line, on site emergency, off site emergency. In case of US-FDA 21 CFR part 212 (1) deals with technical terms meanings for acts, active pharmaceutical ingredients, batch, batch process and control record, component, conditional final release, final release, in active ingredients, in process material, lot, lot number, master production and control record, PET, PET drug, PET drug product, PET drug production facility, production, quality assurance, receiving facility, specifications, strength, sub-batch and verification, whereas the definition of the MSIHC rules, which covers over all application of different sectors of industries but in this review article we have mainly focussed on the applying of various definitions to the pharmaceutical industry in India.

Rule Three deals with the various duties of the authorities, 3 (a). Where the consent authority will inspect the site once in the calendar year. 3 (b). In an exceptional case, where the occupier may submit the report to the MOEF through the appropriate channel. In this sub rule, the directions specific with respect to the exceptional cases for the submission of the report to the MOEF to be included for the better understanding, which results in more clarity, 3 (c). The other provisional rules, for which the duties of various authorities and their responsibility are listed in column 3 of schedule 5 of MSIHC rules 1989. The US-FDA 21 CFR 1.4 of part I, which deals with the general enforcement regulations of the authorities, its sub sections from a to f, which states the duties of the authorities. Gander (2011) [16] reported that the responsibility of the hazardous risk management in occupational environment depends on the three level. That is 1. regulatory, 2. Industrial responsibility and 3. Individual responsibility. By considering MSIHC rule three, we can say that regulatory authority acts as one of the main pillar for minimizing risk but two other main pillars, which drives the organisational goals for the safer operations and good safety culture, which are in form of Management responsibility is the secondary pillar in an industry and the company responsibility are the employees and contractors are the third pillar, where the individual people in the organisation are trained on all the safety and operational aspects of various equipment's as per the BMR to achieve the organisational goal. The three of the combined pillars, which makes a safer working environment in the pharmaceutical industry. Bartle & Vass (2007) [5] stated that the organisational institutions, which has practised self-regulatory goals have achieved better regulation in Great Britain, which has resulted in the new paradigm shift.

Rule Four deals with the general responsibility of the occupier during industrial activity, 4 (1). The Rules, which are applied to 4 (1) (a). where the rule is applied to the hazardous industries like pharmaceutical industries, which are laid in part I of schedule 1 or column 2 of part II of the same schedule. 4 (1) (b). The manufacturing of the drugs in the pharmaceutical industries should maintain the threshold limits for the quantities of the chemicals stored in the occupational environment, which are listed in the column 3 schedule 2. 4 (2). The occupier should have control over all activities in the plant as per 4 (1). Shall provide evidence, showing that, 4 (2) (a). The occupier must identify the major hazards which may lead to accidents in the pharmaceutical industry, 4 (2) (b). The occupier must take adequate steps, 4 (2) (b) (i). The occupier must take steps to mitigate the hazard, so that we can prevent accidents and their consequences while working in the occupational environment, 4 (2) (b) (ii). The occupier must provide training to the workers for working in the various blocks such as IM block, drying block and FG block for handling of the hazardous chemicals and various ways of handling the different kind of the reactions, which are used for the manufacturing of the various consented drugs in the pharmaceutical industry. Further we must maintain antidotes in the occupational health center (OHC). The US-FDA 21 CFR part 211 of section 211.28, which states the personnel responsibilities under sub sections a to d, which includes manufacturing, processing, clothing, personal hygiene, and supervisory control. It is very much necessary to provide high quality drugs, which are useful in treating an injured person in the occupational environment of the pharmaceutical industries (Chowdhury *et al*., 2015) [9].

Rule Five is the notification of the major accidents, 5 (1). It states that any of the major accidents such as blast, fire, and explosion of the process equipment, which has resulted in the loss of life of the human beings or damage of the equipment's while manufacturing the consented drugs in the pharmaceutical industry should be reported to the concern authority as identified in the schedule 5, the major accidents should be furnished within 48 hours to the directorate of

factories of the concerned state department. Further notification to be provided to the concerned different authorities, which are listed in schedule 5 based on the type of major accident. The reporting of the major accidents is to be done as per schedule 6. 5 (2). The concerned authority will investigate the accidents with respect to rule 5 (1) and he will fully analyze the report for the various causes of the accidents, finally it will be submitted to the MOEF within 90 days through an appropriate channel. The European union has implemented information technology (IT) enabled plat form, which is known as early warning response system (EWRS), where the potential exposure of health risk caused due to the chemical exposure from the chemical and pharmaceutical industries leading to the various incidents / accidents, which causes the public threat can be easily identified at early stage (Orford *et al*., 2014) [31]. Such type of technique alerts the risk of the exposure in the region, so that we avoid restricting the exposure caused due to the vapors, hazardous fumes, corrosive atmosphere, which has resulted due to an incident or an accident in the occupational environment. Although notification of the major accidents is mandatory as per MSIHC rules but modernizing with IT platform gives a cutting edge for quicker identification of the major accidents through online alerts, so that the public at large can be aware about the accidental situation, so that the occupier declares as an offsite emergency. 5 (3) states that the occupier must take such measures that similar accidents will not be repeated in the occupational environment. 5 (4). A copy of the accidental report should be available with the occupier, which has been sent to the MOEF through the appropriate channel. 5 (5). The authority writes to the occupier regarding recommendations or the changes to be made to avoid major accidents in the occupational environment of the pharmacytyical industry. The major accidents can be avoided by following appropriate behavior in the working environment. The study was conducted in a chemical company in Bangalore, India after giving training in the various behavioral based safety (BBS) aspects. It was observed that interdependent behavioral had a positive effect in avoiding the incidents / accidents in the working environment, where are independent behavior is used for restricting the spread of COVID-19 by following the golden rules, which are recommended by the WHO. In this way two different types of behaviors were dominant in the chemical industry by following BBS system (yudhsitra kumar, 2022). As per US-FDA 21 CFR section 803.3 (2), which states that any of the reportable events to be reported within 30 calendar days or in five working days to be submitted to the concern authority in accordance with section 803.53 (b).

Rule Six, the Industrial activity**,** which covers the rules from 7 to 15 as per MSIHC rules 1989. 6 (1). The rules are applied to 7 to 15. 6 (1) (a). The hazardous quantity of chemicals, which are used in the pharmaceutical industries are listed the column 2 of schedule 3, where its threshold limits are specified in the column 3, which apples to the rule 5, 7 to 9 and 13 to 15, whereas the column 4 applies to the rule 10 to 12. 6 (1) (b). The hazardous chemicals, which are to be isolated and kept in the tank farm area of the pharmaceutical industry is listed in the column 2 of schedule 2 and its threshold limit of the quantities are listed in the column 3, where the rules of 4, 5, 7 to 9 and 13 to 15 will apply, whereas the column 4 of the same schedule, which applies to the rule 10 to 12. 6 (2). For the purpose of the rule 7 to 15. 6 (2) (a). Any of the new activity in the pharmacytyical industry should commence as follows. 6 (2) (a) (i). The block operations of the pharmaceutical industry should be started only after complying with the MSIHC rules. 6 (2) (a) (ii). In case the intermediate block operations are started before complying with the MSIHC rules, it will be covered under the MAH. A similar rule is applicable, where the modification in the equipment of the process has been made in the drug manufacturing facility without informing the concerned authority. 6 (2) (a) (iii). In the case if we consider an existing industrial activity, it refers to having no changes in the drug manufacturing facility of the industry, which is not a new industry. According to the legal over view of CSA of the federal government, which is released by the 116th congress in the year of 2019 have given certain rules for handling of the hazardous chemical substances and they have imposed penalties for keeping the unauthorized chemicals and their quantities (Campos *et al*., 2019) [7], further in the updated document in the year of 2023, the legal over view of the CSA by the 118th congress, which states that many of the legal drugs are synthetically manufactured in America (Lampe, 2023) [26]. In case of MSIHC rules 1989 that does not have any penalties in the form of various section for the unauthorised possession of the hazardous chemicals or exceeding the legal threshold limit as per the schedule 2 of column 3, 4 and schedule 3, Part I of column 3, 4 but the concern authority has legal right to act and cancel the authorization of the occupier for the manufacturing the pharmaceutical drugs by issuing a notice.

Rule Seven, which deals with the approval and notification of the sites**.** 7 (1)**.** In case the occupier must perform any of the activity in the different blocks, he has to submit a request authorization for permitting the operations for the manufacturing of the drugs by submitting schedule 7 to the concern authorities before three months of the commencement of the operations of the pharmaceutical industry. 7 (2). The concerned authority must approve the documents, which are submitted by the occupier, within 60 days of receipt of the same. In case the documents are not according to the various rules of MSIHC, in this scenario the authority can issue notice to the occupier according to rule 9. All the manufacturing of the pharmaceutical industries uses hazardous chemicals in the form of raw materials to deliver different intermediate, which finally forms of a consented drug. These drug innovation, which passes through many stages such as kilo lab to pilot plant to large scales, which consist of various operational equipment's like reactors, centrifuges, dryers, Jet milling and multi milling, all this equipment are used for manufacturing of the drugs in the pharmaceutical industry (Daemmrich, 2017) [10]. In case of US-FDA part C – building and its facilities as per part 211 of CGMP, which covers design and construction, lightning, ventilation, air filtration, air heating and cooling, sewage and refuses, washing and toilet facility, sanitation and maintenance. Similarly, part D deals with the manufacturing equipment, which consist of equipment size, design, location, construction of equipment, cleaning of the equipment and maintenance, automation, mechanical, electrical equipment

and filers. The electronic common technical document (eCTD), version no 4 came into existence in the year of 2022 [12] for the electronic submission of the regulatory document with the specific guidelines for the pharmaceutical products, which were developed by the centre for drug evaluation and research, US-FDA (eCTD, 2022) [12] but as per the MSIHC rules the occupier in the pharmaceutical companies in India must submit an hard copy as per the rule 7 (1), which will be authorized as per rule 7 (2) by the authority for the operations of the drug in the manufacturing facility. Finally, these drugs when they are manufactured in the Indian pharmaceutical industry, the drugs are to be authorized and approved by the CDSCO in India to sell it in the Indian pharmacy to its various whole Salers and retailers. It is mandatory for the Indian pharmaceutical industries will be audited by the various global drug authorisation bodies before it gives the approval for marketing of their drugs to their country, in this regard Mulaje *et al*.,2013 [30] reported the various history, policy, administration regulated rules for getting the approval licence for selling drug to the different countries of world like USA, China, Europe, Australia and India.

Rule Eight is updating of the site notification by following the threshold quantity – After getting approval according to the rule 7 (1), it is very much necessary that any of the changes in the product mix or any of the changes in the quantity, which is ether decrease or increase in threshold quantities of the chemicals to be informed to the concern authority before starting the process or manufacturing of the consented drug. The US-FDA 21 CFR section 211.42, which covers the design and construction facility, its sub-section 211.42 (1), which states about the receipt, identification, storage and withholding of the usage of the component, which refers to the ingredients used for the manufacturing of the drug. There are no details about the standards chemicals and threshold quantity and the exposure levels of such chemicals used for manufacturing of the drugs has not been included in the US-FDA regulation but the exposure limits with respect to the various chemicals has been covered by other federal agencies such as occupational safety and health administration (OSHA), national institute of occupational and health (NIOSH), American conference of government industrial hygiene (ACGIH), which are in the form of permissible exposure limit (PEL), recommended exposure limits (RELs) and threshold limit values (TLVs), which are used globally for knowing the exposure limits of hazardous chemicals (Kirkpatrick, 2023; Graham *et al*., 2020; Ganio *et al*., 2018) [17, 18, 23].

Rule Nine deals with transitional provisions, 9 (1). The pharmaceutical company occupier should have control over the operation for manufacturing of the consented drug, which are reported under rule 7 (1) or 9(2). After getting the approval from the concern authority, the occupier should commence the manufacturing of the consented drug within six months from the date of the receipt of the approval. The occupiers should furnish the compliance report with respect to the submitted document of schedule 7 within 3 months of the commencement of the operations. The US-FDA 21 CFR 211.100, which covers the written procedure for the manufacturing of the drug and its deviations. The US-FDA 21 CFR 211.100 (a) states that the process of the manufacturing of the drugs should have a BMR and all these documents should represent the highest process, which have been used to achieve the drug quality and its assurance, these documents should be approved by the quality control and assurance department. Any of the changes which are made in the process which affect the yield of the drug should be initiated only by appropriate change control through the quality and assurance department. According to US-FDA 21 CFR 211. 100 (b) states that any of the deviations in the process to be recorded should be properly justified for achieving the highest quality of the drug through proper channel. The fourth industrial revolution of the pharmaceutical industry is using modern technology like internet of things (IoT), artificial intelligence (AI), robotics, and advanced computing to increase their precession of the yield and gets the desired quality of the drug by maintaining the highest safety precautions during the operations and reduce the hazardous waste during the manufacturing process (Mukhlas *et al*., 2022; Arden *et al*. 2021; Tilley, 2017; Baur *et al*., 2015) [3, 6, 29, 41].

Rule Ten is the Safety Reports, 10 (1). The new occupier should commence the drug operation in the various blocks only after preparing the safety report as per schedule 8. 10 (2). It is necessary that the occupier should send a safety report within 90 days of the commencement of operations in the blocks of the pharmaceutical industry. 10 (3). In case of the existing occupier, he should discuss with the authority and prepare a safety report within one year from the date of the commencement of the drug manufacturing operations as per the MSIHC rules. 10 (4). The new and the existing occupier must update the safety report every year with the help of a competent person who is an expert in safety audit field, and he should not be associated with drug industrial activity. 10 (5). The occupier must submit the third-party safety report within 30 days after completion of such report. 10 (6). The occupier must update the safety report every year and shall submit the hard copy to the concern authority within 30 days of commencement of the activity. 10 (7). The authority after going through the safety report, he has a right to issue a notice under rule 19 within forty-five days submission of the safety report for improving the safety aspects of the pharmacytyical industry. The safety report, which covers the safety of Men, Material, and Machinery, which is in the form of 3M. The men use administrative control such as personal protective equipment (PPE) while handling the hazardous chemical materials, operational safety control is used during the operations of the operational equipment / machinery to get the desired output in the pharmaceutical industry by performing proper risk assessment (Teh *et al*., 2019) [40]. The safety reports must contain various hazard mitigations recommendations, which plays a vital role in the pharmaceutical industry, which results in a risk management approach (Dunn *et al*., 2020; Warnasooriya, & Gunasekera, 2016) [11, 43]. The operators will follow the instructions, which are given in the BMR, to get the desired API final products. Good safety principles, which drive the good safety culture in the pharmaceutical industry (Edwards *et al*., 2007) [13]. The safety recommendations and its compliance will have a positive safety culture in the organisation (Agata & Susan, 2018) [1]. The US-FDA, which reviews the safety and quality of the drugs, which are manufactured in the pharmaceutical industry. In case of the new drugs, which are manufactured

should follow a procedure known as premarket approval or it is also known as preapproval review with respect to the safety and quality of the drug. Then US-FDA acts on the issuance of the post market or post approval regulatory procedures to market their products.

Rule Eleven deals with the updating of the reports under rule 10, 11 (1). where the submission of the safety report of the pharmaceutical industry is according to the sub rule (1) of rule 10, the occupier should not make any modification, which affects the submitted safety audit report to the authority. Any such modification should be updated in the safety report of the pharmaceutical industry and should be submitted to the authority by the occupier at least ninety days before the modifications are made. 11(2). After the occupier submits the safety report according to sub rule (1) of rule 10 to the concern authority while continuing the operations in the pharmaceutical industry, within the three years of last submitted of the safety report, the occupier should improvise the technical requirements, which helps in improving the operational safety aspects and mitigate the hazard. The occupier shall send a safety report copy of the pharmaceutical industry to the concern authority after identifying the improvements within thirty days. Any of the changes, which are made in the procedure to made as per US-FDA 21 CFR part 211, which states that the written procedure to be recorded and to be approved by the quality control and assurance department by not affecting the drug yield and its safety. The conceptual changes, which are recommended while handling of the process in the various safety aspects play a vital role in the pharmaceutical industry in improving risk management approach during the operations (Zhang *et al*., 2023) [47].

Rule Twelve, which deals with the requirement for further information to be sent to the authority. The occupier sends the safety audit report as per rule 10. After thoroughly going through the concern safety report by the authority relating to the various operational equipment safety, handlings of the hazardous chemicals used in the operations for manufacturing of the API drugs, the authority may provide notice for any of the clarification requirement and additional information regarding the safety concerns, which he may have. The identified safety concerns to be replied to the concerned authority by the occupier within ninety days of receipt of such notice.

Rule Thirteen, Preparation of the on-site emergency plan by the occupier. 13 (1). It is a plan prepared by the occupier to tackle eventuality during fire, explosion, flood, hurricane and leakage of the hazardous gases in the occupational environment in the pharmaceutical industry. It should also include the chemicals which are present in schedule II. 13 (2). The occupier must ensure that the on-site emergency plan has been prepared as per sub rule 1 of rule 13. Any of the modifications which are made in the on-site emergency plan should be aware to all the occupants of the pharmaceutical industry and it should be useful in tackling an on-site emergency. 13 (3). The on-site emergency plan should be updated as per sub rule 1 of rule 13 by the occupier. 13 (3) (a). An on-site emergency should be made ready before the commencement of the various block operations. 13 (3) (b). In the case of an existing pharmaceutical company, in that scenario, it should be prepared within 90 days of commencing of the operations as per the MSIHC rules. 13 (4). The occupier of the pharmaceutical industry must conduct mock drill every six months once, to tackle the emergency. 13 (5). A detailed report of the mock drill is to be prepared and it should be kept ready as per sub rule 4 of rule 13, so that same can be shown to the authorities during inspection. In case of the mock drill, which are to be practiced in the pharmaceutical industry, which requires two types of skills to tackle the onsite emergency situation are soft skills and technical skills, which are in the form of twelve C

Soft skills

1. Command during the deceleration of the on-site emergency in the occupational environment of the pharmaceutical industry.

2. Communication, which are of two types, they are vertical and horizontal.

Vertical communication: Communication, which is done through telephone, internet and walk talky during the on-site drill for tackling the emergency in the pharmaceutical industry.

Horizontal communication: The emergency communication signals, which are given through siren, megaphone, and sound flasher.

3. Coordination with different teams to tackle emergencies during the mock drill is listed below.

a. Firefighting team
b. First aid team
c. Communication team
d. Rescue team.
e. Evacuation team
f. Security team

4. **Clarity regarding the task:** The scenario of the task to be performed during the mock drill should be aware by all the individuals who are working in the occupational environment of the pharmaceutical industry.

5. **Confidence:** There should be a higher level of confidence while practicing the mock drill. Confidence mainly depends on education, work experience, practice with experience, skills and knowledge.

6. **Competence:** The mock drills, which are practiced should be applied to the real time situation arises and the occupants in the pharmaceutical industry should gain the awareness and knowledge for tackling the emergency scenarios.

Technical

7. Caring towards the injured person
    a. Evacuation
    b. Rescue operation.
    c. Firs aid
    d. Ambulance

8. **Containment:** Following the process safety management (PSM), which includes the isolation of the process equipment's during the emergency arises, so that we can restrict the spread of the onsite emergency to the practiced while conducting the mock drill,

9. **Confinement (Limited towards the release during the emergency drills):** During the practice of the mock drills while opening the hydrant system or sprinkler or foam or water mist or dry chemical powder to be collected in the confinement zones such as dikes, so that it will not get contaminated mixing into rainwater or stormwater collection pit.

10. **Control:** There should be control of the situation to be practiced in the mock drill in case an emergency arises. The practice of the mock drill should include venting of the poisonous gases by scrubbing and tackling emergency by nitrogen blanketing.

11. **Chronology to be maintained:** sequence of the mock drill to be maintained, resulting in achieving the best results for tackling the real time situation, by tackling the emergency in the form of action and its delivery.

12. **Connectivity:** Practicing of the mock drill should full fill the objective of tackling the emergency in real time disastrous circumstances like floods, fire, release of the poisonous gases and explosion of the process equipment's in the pharmaceutical industry (Watson *et al*., 2023)

During the mock drill, the occupier must ensure that the incident observer communicates to the site controller to tackle an on-site emergency, the chain of communication through various emergency controllers for tacking the incident, which are given in the Fig. 2. The on-site emergency mock drill for the chlorine storage facility has been conducted by Soman & Sundararaj (2015) [38] and Xiong *et al*. (2023) [44] have conducted a review on the application of the emergency planning and preparedness in China.

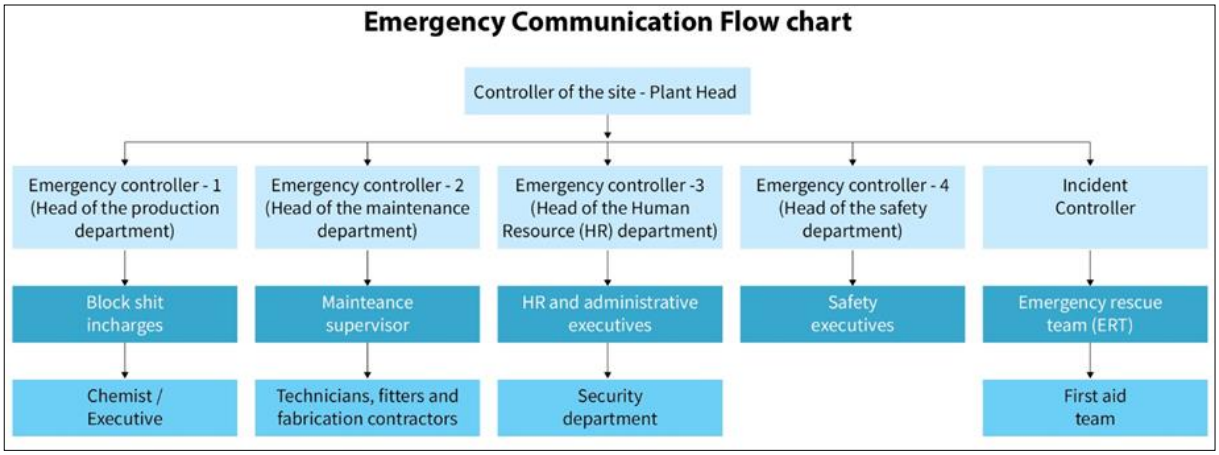


Fig 2: Emergency communication flow chart for tackling the onsite emergency of the pharmaceutical industry

Rule Fourteen is the preparation of the Off-site emergency plan by the authority. 14 (1). where the duties of the authority as identified as per column 2 of schedule 5 to prepare and update the off-site emergency plan, which contains particulars as per schedule 12. To deal with major accidents, which cause extensive damage to the property and human beings in the pharmaceutical industry and there are chances that it may escalate out of the company premises. In this regard the authority will prepare an off-site emergency plan based on interaction with the occupier and other concerned persons who can help them in preparing the off-site plan. 14 (2). To enable the off-site emergency plan, the concern authority prepares the offsite emergency plan as per sub rule 1 of rule fourteen. The occupier must provide the full required information of the process and handling of the hazardous chemicals and likely scenarios, which may result in an off-site emergency leading to a major accident and destruction of the property. Finally, the authority will provide the offsite emergency plan, which relates to the duties of rule 13. 14 (3). The concerned authority should prepare the off-site emergency plan of sub rule 1 of rule fourteen. 14 (3) (a). The off-site emergency plan to be prepared before the commencement of the new activity to be carried out in the pharmaceutical industry. 14 (3) (b). In the case of existing pharmaceutical industry, the offsite emergency plan to be enforced within the six months of starting of the operations. 14 (4).

The concerned authority must ensure that a rehearsal for the off-site emergency in the pharmaceutical industry is carried out yearly once. The US-FDA recently released a document in the year 2019, which is known as FDA operation emergency plan, version 3.0, which covers the various ways of tackling in the emergency exists. In this regard, the US-FDA, which has an office of the emergency management (OEM) and they are responsible for updating the emergency plans, which coordinates with the incident command system for training the emergency staff as per the requirements of the national response framework and national incident management system and they actively participate in case of national emergency. Many of the authors such as Ruj & Chatterjee, 2012 [34] has stressed the importance of handling the toxic chlorine gas leakages from the chemical plant, which has resulted in an off-site emergency in India, Kavishwar & Chatpalliwar (2013) [19] have reported the various ways of handling an off-site emergency in case of leakage of the liquified ammonia, Aruru *et al*., (2021) [4] stressed the importance of handling an offsite emergency situation in the pharmaceutical industry during the COVID-19 circumstances and Sami *et al*. (2021) [35] have reported that the global leading pharmaceutical industries have taken highest safety precautions during the COVID – 19 circumstances and they have run their production activities in order to meet their needs of the health care industry.

Rule fifteen is the information to be given to the person liable to be affected by the major accident. 15 (1). The occupier of the pharmaceutical industry should communicate telephonically or directly to the district emergency authority, then he will visit the industry in case of the occurrence of the major accident then 15 (1) (a). He will investigate and assess the nature of the major accident and 15 (1) (b). The various dos and don'ts and safety measures to be taken in case of the occurrence of such a major accident will be stressed. 15 (2). The occupier should follow sub rule 1 of rule 15 and also inform the district emergency authority about the various steps, which are taken to avoid major accidents in the future.

Rule sixteen is the disclosure of information. The authority evaluating the information according to the rule 5 or 7 to 15, the authority passes the information to the other person who is an expert in the field, in that scenario the other person shall not disclose or use the information under the specified rules without the consent of the concern authority. Similarly, the US-FDA 21 CFR 211.16, which deals with the distribution of the records.

Rule seventeen deals with collection, development, and dissemination of information. 17 (1). The rule is applied to the occupier who is managing the use of the hazardous chemicals, which are specified in part 1 of schedule 1, which includes column 2 of part II of the same schedule. 17 (2). The occupier should have over all control of the activities, which are performed in the pharmaceutical industry and their use of the chemicals, which are specified in sub rule 1 of rule 17. The occupier should develop the material safety data sheet (MSDS) for the various chemicals, which are used for the process and its various intermediates, which are generated during the manufacturing of the consented drugs of the pharmaceutical industry as per the schedule 9. The information of the MSDS should be available in the form of n hard copy, so that we can easily understand the properties of the chemicals, type of hazards and its control. The MSDS should be easily accessible to all occupants of the pharmaceutical industry. 17 (3). The occupier while developing the MSDS should ensure all the practical implications, which are involved in the handling of the hazardous chemicals, its usage and tacking an emergency to be included in schedule 9, 17 (4). All chemicals which are stored in the tank farm area of the pharmaceutical industry should have properly labelled for their identification. Which includes, 17 (4) (a). Name of the chemical to be written on the storage tank / container. 17 (4) (b). Name and address of the manufacturer or the importer of the hazardous chemicals. 17 (4) (c). The various physical, chemical and toxicology data with respect to the chemicals, which are used in the process should have a documented procedure whether it is toxic / highly toxic / extreme highly toxic in nature as per part I of schedule I. In consistency with rule 17 and by considering rule 4, it is mandatory that the weighed container is tagged after dispensing of raw materials (RM) through RLF from the stores department. Details of the dispensing quantities of the chemicals should be present in the BMR along with its batch number of the intermediate / final product. The US-FDA 21 CFR Part 211, its sub part G deals with the packing and labelling control, its section 211 (122) deals with the materials examination and usage criteria, 211 (125) deals with the procedure for labelling and issuance of the raw materials and the 211 (130), which deals with the packing and labelling procedure of the various intermediates, which are manufactured in different blocks. The details labeling procedure in the MSIHC 1989 to be included in the rules for better clarity. All the parts of CFR have been listed in the US-FDA portal, which are updated in regular basis, which are considered as world most stringent standard for authorizing the manufacturing of the consented drugs for the pharmaceutical industry.

Rule Eighteen is the Import of hazardous chemicals. 18 (1). This rule is applied for the chemicals, which are used for manufacturing of the consented drug as per part 1 and column 2 of part II of schedule 1. 18 (2). The occupier who is importing the chemicals for manufacturing of the drugs in the pharmaceutical companies in the India should inform the concern authorities with in the 30 days before the chemicals received in India as per the column 2 of schedule 5. 18 (2) (i). Name of the person in India who is going to receive the consignment. 18 (2) (ii). The entry of the chemical in the Indian port. 18 (2) (iii). The Mode of transport and packing of the imported chemicals. 18 (2) (iv). The quantity of the chemical being imported. 18 (2) (v). Safety information of the chemicals, which are imported into the country. 18 (3). The concern authority of the state feels that the imported chemical may cause harm, which may lead to the accident, in that scenario, the occupier will be deemed to take highest safety precautions while importing such type of chemicals in India. 18 (3a). The concern authority of the state feels that the chemicals, which are imported in India, which cause harm to environment and devastating effect considering the safety aspects of importing the chemicals in India. In that scenario, the concerned authority can authorize the instruction to stop the import of such chemicals. 18 (4). In other scenario the concern authority of the state will give directions to the port authority for the safe unloading of chemical consignment, which are received in India. Safe storage procedures are to be followed in the dockyard for chemicals, which are imported for the manufacturing of the drugs in the pharmaceutical industry in India. 18 (5). Any of the occupier who is manufacturing the drugs in the pharmaceutical industry should maintain a register for the import of different kinds of chemicals in India as per the schedule 10, such type of register should be available with the occupier, so that same can be shown to the MOEF authorities during inspection. 18 (6). The importer of the chemical or behalf of the importer should ensure that the hazardous chemicals should reach from the dock yard to the pharmaceutical manufacturing facility in accordance with central motor vehicles rules 1989, which are framed under the provisions of the motor vehicle act 1988. Any of the import of chemicals into the USA should be covered under toxic substances control act (TSCA), as per the section 5 (a), a notice to be submitted to the EPA at least 90 days before importing of a new chemical, the activities should be carried out before pre-manufacturing. The toxic substances control act (TSCA) 1976, section 6, which has an inventory of around 83,000 different types of chemicals, which are imported into the country. The US customs and border protection (CBP), which published a rule in year of December 2016, where there is an option of online submission for obtaining the import certification under

TSCA. TSCA section 13, which deals with the imported chemicals or the mixture, which are refused entry into the USA by the customs authority due to violation of section 5, 6 or 7 of TSCA.

Rule Nineteen delas with improvement notices. 19 (1). where the authority can give improvement notice to the occupiers for the improvements on the safety aspects with respect to manufacturing of the drug in the various block of the pharmaceutical industry within 45 days. 19 (2). The improvement notice issued to the occupier as per sub rule 1 of rule nineteen by the authority, should be complied in all the safety aspects for the safer manufacturing of drugs in the pharmaceutical industry.

Rule Twenty deals with the power of the central government to modify the schedule, where the central government at any time can modify the schedule by official gazette for improving the safety aspects with respect to manufacturing, storage and import of hazardous chemicals. Similarly drugs technical advisory board (DTAB), Drugs Consultative Committee (DCC) and the Central Drugs Laboratory (CDL, Kolkata) are special agencies in India, which are related to the drug regulation. Regarding of any changes in the drug regulation in India, the DTAB a powerful body, which guides for the implementation of the new regulation for the central government, and it also recommended the changes to be made considering present scenarios in the country (Chowdhury *et al*., 2015) [9]

An Overview of the Twelve Schedules as per MSIHC Rules 1989, Which are as Follows

Schedule 1 (Rule 2e (i), 4 (1) (a), 4 (2), 17 and 18) - Part I – I (a). It describes about the lethal toxicity of the chemicals, which are used for the manufacturing of the drugs, the degree of the toxicity with reference to the Oral, Dermal and inhalation toxicity in the occupational environment of the pharmaceutical industry. I (b). Flammable chemicals. I (b) (i). It deals with the Flammable gases, I (b) (ii). Extremely flammable liquid, I (b) (iii). Very extremely flammable liquids, I (b) (iv). Highly flammable liquids and I (b) (v). Flammable liquids. Part II consist of six hundred and eighty-four different chemicals, which are hazardous and toxic in nature used for manufacturing of the consented drugs. Refer page number 734, which deals with part I, whereas page 735 to 744, which deals with Part II of MSIHC rules (MSIHC, 1989).

Schedule 2 (Rule 2(e) (ii), 4 (1) (b), 4 (2) (1) and 6 (1) (b)) - Isolated storage at installations other than those covered by schedule 4 – It consist of four columns, first column consist of serial number, second column consist of list of chemicals, third column consist of threshold limits, which applies to the rule 4, 5, 7 to 9 and 13 to 15 and fourth column refers to the threshold limit, which applies to rule 10 to 12 for the consented drug manufacturing facility. Refer page number 745 to 747 of MSIHC rules (MSIHC, 1989).

Schedule 3 (Rule 2(e) (iii), 5 and 6(1) (a)) – List of hazardous chemicals for application of the rules 5 and 7 to 15 – Part I consist of five columns, first column is the serial number, second column is the name of the chemicals of different groups, third column consist of threshold quantities for the application of rules 5, 7 to 9 and 13 to15 and the column four consist of threshold quantity for the application of the rules 10 to 12 and fifth column is the Chemical abstract series (CAS) number. Part II deals with the group 5 of the flammable substances, which consist of four columns, first is the serial number, second column is the name of flammable substances and columns 3 and 4 are same as part I of schedule 3. Refer page number 748 to 755 and 756 number for Part I and part II of MSIHC rules (MSIHC, 1989).

Schedule 4 (Rule 2 (h) (i)) - It refers to the type of reaction with respect to the organic and inorganic chemicals, which are used in the manufacturing of the consented drug of the pharmaceutical industry. Refer page number 757 of MSIHC rules (MSIHC, 1989).

Schedule 5 (Rules 2 (b) and 3) – It consist of three columns, first is the serial number, second is the authorities with the legal backing and the third column is the duties of the respective authorities involved in the legal aspects of the pharmaceutical industry. Refer page number 758 to 761 of MSIHC rules (MSIHC, 1989).

Schedule 6 (Rule 5 (1)) - Information to be furnished regarding the notification of a major accident, which consist of nine points to be submitted to the concern authority during any of the occurrence of the major accident in the pharmaceutical industry. Refer page number 762 to 763 of MSIHC rules (MSIHC, 1989).

Schedule 7 (Rule 7 (1) – Part I delas with the information regarding the notification of the site to be submitted to the authority. Similarly, Part -II deals with the particular about the changes in the pipeline made by the occupier of the pharmaceutical industry. Refer page number 764 to 765 and 766 for part I and II of MSIHC rules (MSIHC, 1989)

Schedule 8 (Rule 10 (1)) – Details of the safety information report to be furnished by the occupier of the pharmaceutical industry to the concern authority. Refer page number 767 to 769 of MSIHC rules (MSIHC, 1989)

Schedule 9 (Rule 17) – Format of the safety data sheet, which consist of ten sections to be maintained by the occupier who utilises the hazardous chemicals for manufacturing of the consented drugs of the pharmaceutical industry. Refer page number 770 to 773 of MSIHC rules (MSIHC, 1989)

Schedule 10 (Rule 18 (5)) - Format for maintaining records of hazardous chemicals, which are imported for manufacturing of the consented drugs of the pharmaceutical industry. Refer page number 773 of MSIHC rules (MSIHC, 1989)

Schedule 11 (Rule 13 (1)) – Details of the on-site emergency plan to be submitted to the concern authority by the occupier of the pharmaceutical industry. Refer page number 774 to 777 of MSIHC rules (MSIHC, 1989).

Schedule 12 (Rule 14 (1)) - Details to be furnished to the concern authority about off-site emergency plan, which are maintained by the occupier of the pharmaceutical industry. Refer page number 777 to 778 of MSIHC rules (MSIHC, 1989).

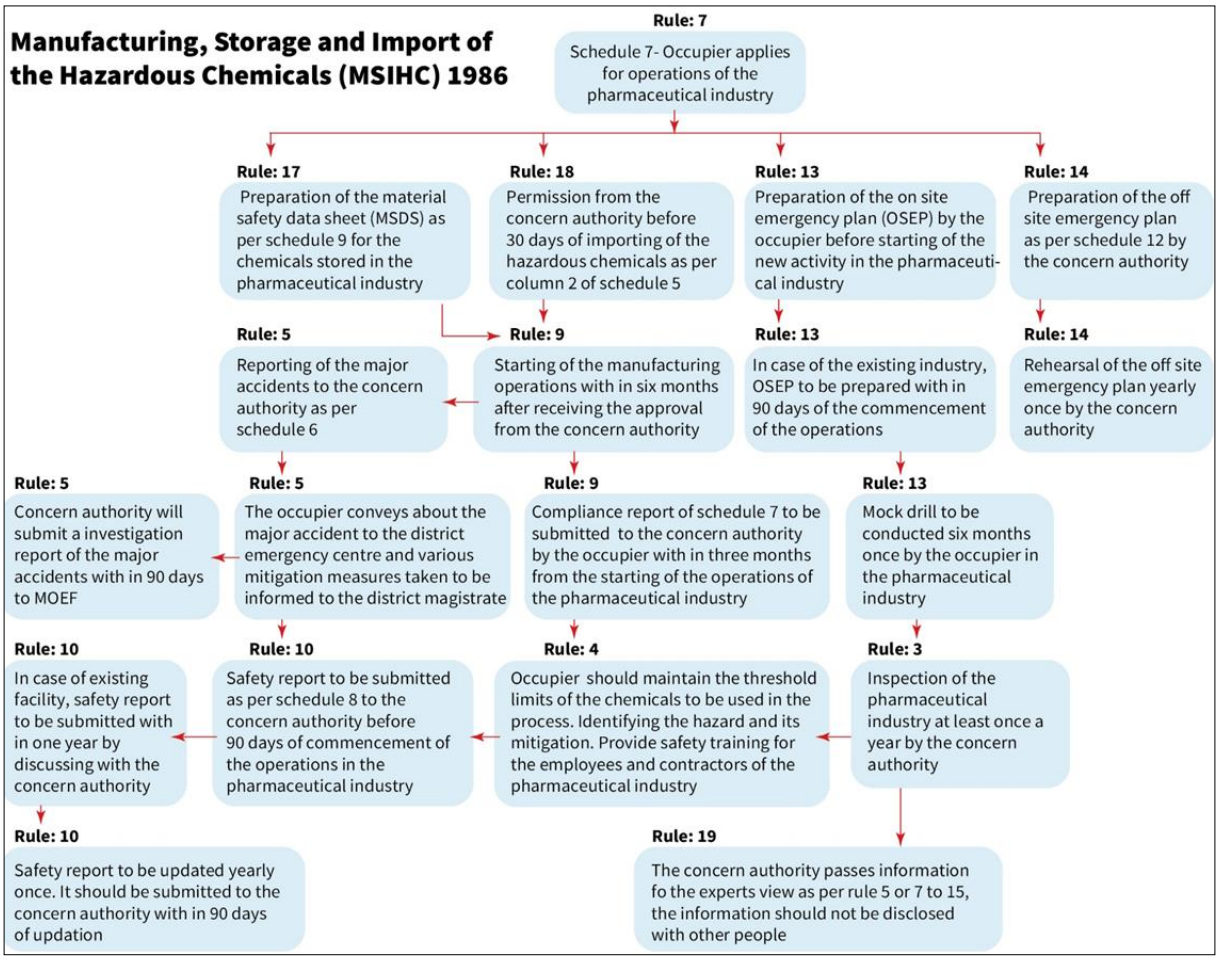


Fig 3: An overview of applying MSIHC 1989 rules to the pharmaceutical industry in India

Conclusion

India is playing an important role in the manufacturing of different kind of drugs for the global community. Presently India is growing at the rate of US$ 3.73 trillion with a gross domestic product (GDP) of 6.3 % against the global average GDP is 2.9 % at the end of the year 2023. India is having the huge potential of growth for the pharmaceutical industry, as it is a leading provider of the lifesaving drugs in the world. In this review article we have presented the importance of applying the MSIHC rules 1989 to the pharmaceutical sector, which covers 20 rules, and an overview of the 12 schedules has been presented. The importance of the US-FDA 21 CFR part 210 and 211 with various sections were correlated with the MSIHC rules. Similarly, the TSCA act of 1976 with the various sections for the import of the hazardous chemicals into the USA were correlated with the MSIHC rules of1989, which are applied to the pharmaceutical Industry in India. The MSIHC1989 rules, which includes the various ways of getting approval for the site, operational facility, handling of hazardous chemicals, hazards and its mitigation, safety report for existing or new industries, updating of safety reports and submitting it to the various authorities, notice for improvements for the operational facility, on site emergency and its updating, mock drill and off site emergency and its rehearsal rules to be followed in the pharmaceutical industry in India have been presented in this review article. An overview of applying the MSIHC rules 1986 [27] to the pharmacytyical industry in India has been presented in the Fig. 3.

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